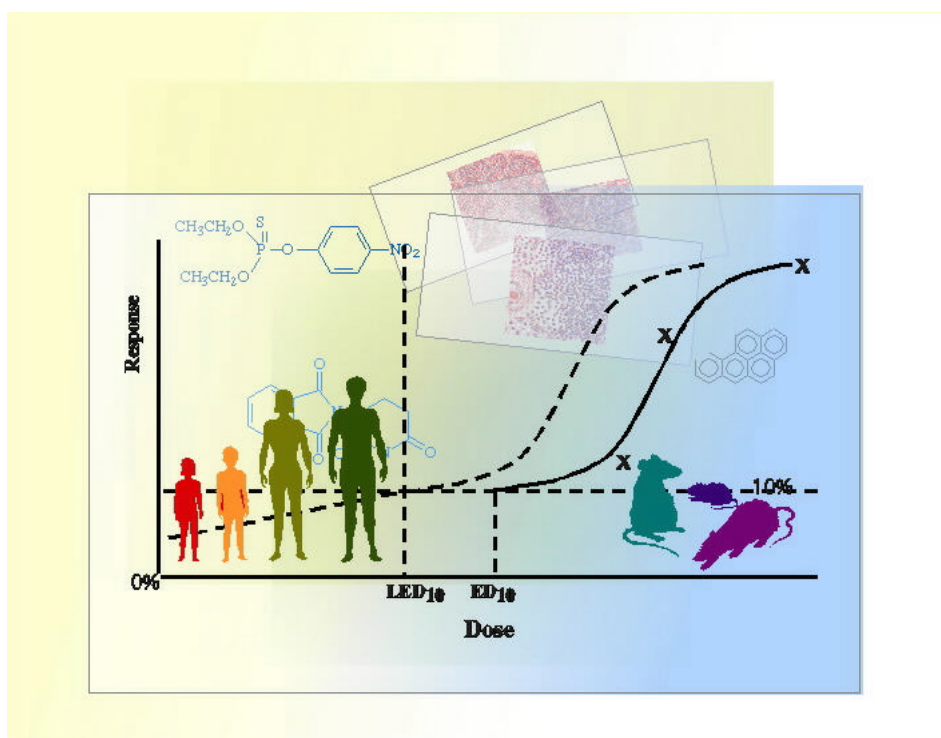


HUMAN HEALTH RISK ASSESSMENT

Methidathion



U.S.

Environmental Protection Agency
Office of Pesticide Programs
Health Effects Division (7509C)
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HUMAN HEALTH RISK ASSESSMENT

Methidathion

Phase 5

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EXECUTIVE SUMMARY

The product/residue chemistry, toxicology, and exposure databases for methidathion are adequate to assess, with reasonable level of confidence, the acute and chronic dietary risks to the U.S. population and other exposed subgroups as well as dermal and inhalation exposure risks to occupational workers from the use of methidathion on agricultural and non-agricultural products.

Methidathion (O,O-dimethyl phosphorodithioate, S-ester with 4-(mercaptomethyl-2-methoxy-1,3,4-thiadiazolin-5-one) is a non-systemic, organophosphate (OP) insecticide registered for control of a broad spectrum of agricultural insect and mite pests on various terrestrial food crops. Use sites include citrus, stone and pome fruits, nuts, artichokes, olives, safflower, sunflower, alfalfa (grown for seed only), and cotton. Methidathion is also used on terrestrial non-food crops such as tobacco and ornamental plants (nursery stock only). Nuts, stone fruits, and citrus are the predominant uses. Novartis, Inc. and Gowan Company maintain the registrations of the manufacturing use products (MUP's); technical grade, 95% active ingredient (ai), as well as an end-use product (EUP), 25% ai wettable powder (WP). Gowan Company also maintains the registrations of the formulated intermediate (FI) 50% ai, and two emulsifiable concentrates (ECs), 22.6% and 24.4% ai. All EUP's are restricted-use pesticides. The two EC product registrations are owned and maintained by Gowan Co. While these products are not marketed or produced at this time the Agency must consider these formulations as part of the total potential risk from exposure to methidathion. Application rates of the WP and EC products range from 0.25 to 5 lbs ai/A. According to the product labels, WP and EC products are registered for the same uses, except for sunflower and tobacco, which is listed on the EC label but not on the WP label. Applications can be made using fixed-wing aircraft, groundboom sprayer, airblast sprayer, low pressure wand and backpack sprayer.

Hazard Identification

The toxicology database is complete and provides evidence that cholinesterase inhibition (ChEI) is the most sensitive toxicological observation in laboratory animals. Technical methidathion has high acute oral toxicity (Toxicity Category I) and moderate acute dermal and inhalation toxicity (Toxicity Categories II and III, respectively). Methidathion is a mild eye irritant (Toxicity Category III), is not a skin irritant (Toxicity Category IV) and is not a dermal sensitizer. Methidathion did not induce organophosphate induced delayed neuropathy (OPIDN) in the hen. In an acute neurotoxicity study in rats, following a single oral dose, methidathion was associated with neurotoxicity in both sexes as evidenced by decreases in maze activity and alterations in functional observation parameters at the highest dose tested (HDT). In addition, there were statistically-significant decreases in plasma, red blood cell (RBC), and brain cholinesterase activity at all dose levels.

In a subchronic neurotoxicity study in rats, following dietary administration, methidathion caused significant decreases in plasma, RBC, and brain cholinesterase activity in both sexes. Following repeated dermal applications to rabbits, ChEI's (plasma, RBC, and brain cholinesterase activity in males and RBC and brain cholinesterase activity in females) was seen under occlusive conditions, but no biologically or statistically-significant ChEI was seen under non-occlusive conditions. Chronic dietary exposure to dogs resulted in inhibition of RBC and brain cholinesterase activity, as well as elevation of hepatic enzymes, gross hepatic lesions, and microscopic presence of bile plugs, distended bile canaliculi, and chronic hepatitis.

No evidence of carcinogenicity was seen in male or female rats; however, there was evidence of carcinogenicity in male mice at the highest level tested (benign and malignant liver tumors were seen). The Cancer Peer Review Committee (CPRC) classified methidathion as a Group C, possible human carcinogen and did not recommend a quantitative risk assessment for human risk characterization. The CPRC deemed that a quantitative cancer risk assessment was unnecessary because the evidence as a whole (i.e., one sex, one species, common tumor type, no increase in proportion of malignant tumors, or apparent shortening of time to tumor) was not considered strong enough to warrant a quantitative estimation of human risk. This was supported by the lack of evidence of mutagenicity under both *in vivo* and *in vitro* conditions.

There was no evidence of increased susceptibility following *in utero* exposures to rats and rabbits as well as pre/post-natal exposure to rats. Additionally, there was no evidence of abnormalities in the development of the fetal nervous system in these studies.

The Food Quality Protection Act (FQPA) Safety Factor Committee recommended that the 10x safety factor for the protection of infants and children should be reduced to 1x because: (1) the toxicology data base is complete; (2) there was no evidence of increased susceptibility seen following *in utero* exposure to rats and rabbits; (3) there was no evidence of increased susceptibility in the offspring in the two-generation reproduction study in rats; (4) there was no evidence of abnormalities in the development of the fetal nervous system in the offspring; (5) there was no evidence for requiring a developmental neurotoxicity study; (6) adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess dietary exposure and to provide a screening level drinking water exposure assessment; and (7) there are no registered residential (home owner) use.

Acute and chronic dietary exposure risk assessments were conducted for the U.S population and various population subgroups including infants and children. Aggregate acute and chronic risk assessments addressed the potential dietary exposure to methidathion residues from food and drinking water. Because there are no registered uses of methidathion in residential settings, the aggregate assessment for the general population and specific subgroups includes only food and water exposures. Risk assessments were also conducted for dermal and inhalation exposures to occupational pesticide handlers (mixers/loaders/applicator) as well as for workers during postapplication activities.

For acute dietary risk assessment, a NOAEL of 0.2 mg/kg/day established in the subchronic neurotoxicity study in rats was selected. The NOAEL was based on significant plasma, RBC and brain ChEI seen at 0.6 mg/kg/day (LOAEL). An Uncertainty Factor (UF) of 100 was applied to the NOAELs to account for intraspecies extrapolation (10x), interspecies variation (10x), and the FQPA safety factor (1x). **The acute Reference Dose (RfD) was 0.002 mg/kg/day.**

As per current OPP policy, the RfD modified by the FQPA safety factor is referred to as a Population Adjusted Dose (PAD). Since the FQPA safety factor is 1x, the RfD is numerically equal to the PAD.

For chronic dietary risk assessment, a NOAEL of 0.15 mg/kg/day, established in the chronic toxicity study in dogs, was selected. The NOAEL was based on significant RBC, and brain ChEI seen at 1.33 mg/kg/day (LOAEL). A UF of 100 was applied to the NOAELs to account for intraspecies extrapolation (10x), interspecies variation (10x), and FQPA safety factor (1x). **The chronic RfD was 0.0015 mg/kg/day.**

For occupational dermal exposure risk assessments to pesticide handlers (mixers/loader/applicators), a NOAEL of 20 mg/kg/day established in the 21-day non-occluded dermal toxicity study in rabbits was selected. No systemic toxicity was seen at this dose, the HDT. For occupational dermal exposure risk assessments to workers involved in postapplication activities, an oral NOAEL of 0.2 mg/kg/day (from the subchronic neurotoxicity in rats) adjusted for 30% dermal absorption factor was selected. Occupational inhalation exposure risk assessments were also conducted with the oral NOAEL of 0.2 mg/kg/day from the rat subchronic neurotoxicity study. Risk assessments for long-term dermal or inhalation exposures were not conducted since the typical use pattern (one to two applications/year) does not indicate the potential for long-term exposures via these routes. **For occupational exposure risk assessment, a Margin of Exposure (MOE) of 100 or greater does not exceed the Health Effects Division's (HED) level of concern.**

Dietary Exposure and Risk Characterization

The acute dietary risk assessment, based on probabilistic exposure analysis (Monte Carlo), indicates that methidathion residues in the diet do not exceed HED's level of concern for any of the population subgroups examined. The highly refined assessment, based on an acute PAD of 0.002 mg/kg and conducted at the 99.9th percentile of exposure, revealed that the percentages of the acute PAD occupied ranged from 14% for females (13+,nursing) to 64% for children (less than one year of age). Percent crop treated data, USDA Pesticide Data Program (PDP) monitoring data, and field trial data were used in this assessment. **The acute dietary exposure to methidathion from its pesticidal use does not exceed HED's level of concern.**

The chronic dietary risk assessment was partially refined, using both percent crop treated data and anticipated residues. The percent of the chronic PAD occupied from dietary exposure to residues of methidathion ranged from 3% for females (13+,nursing) to 23% for children (one to six years). This assessment was based on a chronic PAD of 0.0015 mg/kg/day. **The chronic dietary exposure to methidathion from its pesticidal use does not exceed HED's level of concern.**

The Environmental Fate and Effects Division (EFED) provided a screening level assessment using simulation models and limited monitoring data to estimate the potential concentration of methidathion in ground and surface water. Estimated environment concentrations (EECs) were obtained for ground and surface water by Tier I, SCI-GROW model for ground water and Tier II, PRZM-EXAMS model for surface water. **The EECs were 0.4 ppb in ground water, and 5.6 ppb and 0.6 ppb, respectively, for the acute (peak) and average (56-day) in surface water.** These concentrations are supported by limited California surface and ground water monitoring data. Because dietary risk assessments based on exposures solely from food do not exceed levels of concern, both acute and chronic drinking water levels of comparison (DWLOCs) were calculated and compared to the EFED model estimates and monitoring results. **For the most sensitive subgroup (children <1 year), the acute (7.2 ppb) and the chronic (13 ppb) DWLOCs do not indicate a risk concern from potential exposure to methidathion residues in drinking water.**

For methidathion, the aggregate risks are limited to food and water exposure, as there are no residential uses. Both the acute and the chronic dietary (food) risk estimates, risk estimates for methidathion exposure, were less than 100% of the acute and chronic PAD's. Additionally surface and ground water acute and chronic EECs did not exceed the DWLOC. **Therefore, aggregate acute and chronic dietary risk estimates associated with consumption of methidathion in food and water do not exceed HED's level of concern.**

Occupational Handler Exposure and Risk Characterization

Occupational exposure risk assessments for handlers (mixer/loaders/applicators) were based on Pesticide Handler's Exposure Database (PHED); and MOE's were calculated for dermal and inhalation exposures. An MOE of 100 or greater does not exceed HED's level of concern. A total of 12 major exposure scenarios were identified for handlers during mixing, loading, and applying products containing methidathion to agricultural crops. Of the 12 scenarios, 11 have MOE's greater than 100 with minimum personal protective equipment (PPE) [with water soluble packets (WSP), single layer clothing (SLC) which includes long sleeve shirt, long pants, shoes and socks and gloves], or with additional PPE's, [that include WSP, coverall over SLC (i.e, double layer clothing (DLC)], gloves and dust/mist respirator] or with engineering controls [WSP, SLC, gloves, and closed cabs]. **For one remaining scenario (*mixing/loading in support of aerial application*), risk estimates are of a concern** since even with engineering controls, the MOE's for **dermal** (MOE=91) and **inhalation** (MOE=95) are below the required MOE of 100 (HED's level of concern).

Because the dermal and inhalation NOAELs are based on different toxicological endpoints (i.e., lack of systemic toxicity via the dermal route and ChEI via the oral route), it is inappropriate to combine the exposures for these pathways. Therefore, only route-specific MOE's are appropriate for evaluation. However, since ChEI is the principal toxicological endpoint of concern for OP's via the dermal and inhalation routes, an analysis of the total MOE's was conducted for risk characterization purpose only. The combined exposure (dermal+ inhalation), resulted in MOE's that were less than 100 for two additional exposure scenarios for which the route specific MOE's were greater than 100: *mixing/loading WSP in support of aerial application* (Dermal MOE = 140; Inhalation MOE = 170; Total MOE = 77) and *liquid aerial application with a fixed-wing aircraft* (Dermal MOE = 150; Inhalation MOE = 120; Total MOE = 67).

Occupational Postapplication Exposure and Risk Characterization

There is considerable potential for postapplication occupational exposure to methidathion residues. The results of the Dislodgeable Foliar Residue (DFR) studies conducted with methidathion on cotton and citrus crops indicate that workers (i.e., scouts, pickers) require entry restrictions or reentry intervals (REIs) before engaging in postapplication activities. Postapplication risks were estimated using crop-specific DFR data for citrus and cotton. The combined results of citrus DFR studies conducted in California and Florida were used for safflower scouting and irrigation, as well as for artichoke cultivation and harvesting. An MOE of 100 or greater does not exceed HED's level of concern.

For cotton scouting in North Carolina and Texas, the REIs are one day after treatment (DAT) for early scouts, and for late scouts the REIs are at six days after treatment and seven days after treatment in North Carolina and Texas, respectively.

Based on a DFR study in citrus, the REI is 24 days after treatment for citrus harvesting.

Translating the dissipation rate from the submitted citrus and cotton DFR studies data, a REI of 2 days was obtained for scouting and irrigating safflower, while a REI of 15 days is required for cultivating/harvesting/packing artichokes.

For other crops, the REIs ranged from 17 to 34 days, depending upon the crop and postapplication activity.

It was determined from labeling that methidathion is applied prior to foliation or at budding to all other tree crops (stone and pome fruit, nuts, and olive trees). Therefore, there should be no foliar residue present, *per se*, during harvesting. Based on these agricultural practices, HED has concluded that there should be negligible postapplication methidathion chemical exposure to workers from tree crops other than citrus.

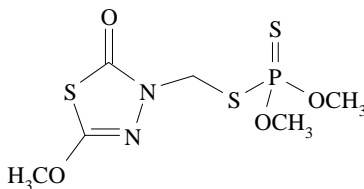
There are no registered uses of methidathion at the present time that could result in residential exposures. The Agency recognizes that there are many issues related to the use of agricultural chemicals in the general population, i.e., spray drift exposures and exposures to farm worker children and farm residents. The Agency is in the process of developing guidance and procedures for characterizing these kinds of exposures. An assessment of the potential exposure and risk from these kinds of exposure associated with the agricultural use of methidathion are not addressed in this document.

SCIENCE ASSESSMENT

I. PHYSICAL AND CHEMICAL PROPERTIES

A. Description of Chemical

Methidathion (O,O-dimethyl phosphorodithioate, S-ester with 4-(mercaptomethyl-2-methoxy-1,3,4-thiadiazolin-5-one) is an insecticide/acaricide registered for control of a broad spectrum of agricultural insect and mite pests on various crops, predominantly alfalfa, citrus, and cotton.



Molecular Weight:
CAS Registry No.:
Shaughnessy No.:

Empirical Formula:

C₆H₁₁N₂O₄PS₃
302.3 g/mole
950-37-8
100301

B. Identification of Active Ingredient

Methidathion is a colorless to white crystalline solid with an OP odor and a melting point of 39-40 C. Methidathion is slightly soluble in water at 240 ppm (20 C), and is soluble in benzene, acetone, methanol, and xylene at >60 g/100 mL (25 C). Methidathion is only moderately soluble in chloroform and dichloromethane.

II. HAZARD ASSESSMENT

A. Toxicology Assessment

The toxicology database for methidathion is complete and will support reregistration.

1. Acute Toxicity

The acute toxicity data on technical methidathion are summarized in Table 1.

Table 1. Acute Toxicity of Technical Methidathion

Study Type	MRID	Results	Toxicity Category
Acute Oral - Rat	00139328	LD ₅₀ = 46.1 mg/kg	I
Acute Dermal - Rat	00139326	LD ₅₀ = 1663 mg/kg	II
Acute Inhalation - Rat	00011449	LC ₅₀ = 19 mg/L/1hr	III
Primary Eye Irritation - Rabbit	00159199	Mild irritant	III
Primary Skin Irritation- Rabbit	00159200	Non-irritant	IV
Dermal Sensitization - Guinea Pig	00252433	Non-sensitizing	NA
Acute Delayed Neurotoxicity - Hen	00011704	NOAEL = 350 mg/kg Negative for OPIDN	NA
Acute Neurotoxicity - Rat	43145903 43590304	ChEI: NOAEL = < 1 mg/kg Neurotoxicity: NOAEL = 4 mg/kg LOAEL = 8 mg/kg. No neuropathology	NA

In Phase 1 of an acute oral toxicity study, methidathion (a.i. 93.2%) was administered to 5 SD rats/sex/dose in corn oil (5 mL/kg) by gavage at a single dose level of 3, 5, or 10 mg/kg, and to two other male groups (5 each) at 10 or 35 mg/kg and to a group of five females at 20 mg/kg. All five male rats in the 35 mg/kg group and 4/5 females in the 20 mg/kg group died within three days of dosing. All other animals in all groups survived the 14 day observation period, and these animals did not seem to experience dose-dependent body weight changes during this time. Within one to four hours of treatment, animals at the 5 mg/kg or higher doses experienced one or more signs of cholinesterase poisoning such as miosis, hypoactivity, tremors, salivation, dyspnea, red-stained face, and absence of pain reflex. Also, there were sporadic incidences of soft stool that seemed to be due to the oil vehicle. The NOAEL was 3 mg/kg based on finding miosis in 3/5 males and yellow-stained urogenital area in 1/5 females within the 5 mg/kg (LOAEL) (MRID 44434501).

In Phase 2 of this acute oral study, methidathion (a.i. 93.2%) was administered to 5 SD rats/sex/dose in corn oil (5 mL/kg) by gavage at a single dose level of 0, 0.5, 1.0, 2.5, 5.0, or 10.0 mg/kg (groups one through six, respectively) and all animals were killed four hours later. There were sporadic incidences of soft stool in all groups (probably due to corn oil); however, no other signs of clinical toxicity were reported in groups one to five. Some of the animals within group six experienced one or more signs of Cholinesterase poisoning including tremors, salivation, and absence of pain reflex. When tested at four hours following test chemical administration, there was a dose-dependent inhibition in Cholinesterase activity where, based on statistically-significant differences, the NOAEL/LOAEL for brain, plasma, and RBC were 2.5/5.0, 2.5/5.0, and >10/>10 mg/kg in males and 1.0/2.5, 5.0/10.0, 2.5/5.0 mg/kg, in females, respectively. Under the conditions of the Phase 2 study, the NOAEL is 1 mg/kg and the LOAEL is 2.5 mg/kg, based on brain Cholinesterase inhibition in female rats.

2. Subchronic Toxicity

In a dermal toxicity study, groups of New Zealand rabbits (5/sex/dose) received repeated dermal applications of methidathion (technical, 95%) in polyethylene glycols 400 at dose levels of 0, 1, 10, 40, or 80 mg/kg/day, six hours per day, five days per week for 21 days. The test material was applied (3 mL/kg) to the skin under an occlusive rubber binder which was fastened with tape. Controls received the vehicle and dressing without the test compound. Mortality occurred in males at all treatment levels and starting from 10 mg/kg/day in females. No dermal irritation was seen at any dose level. The primary clinical signs of toxicity were consistent with ChEI and included tremors, anorexia, bloating, hunched posture, languidity, altered respiration, and soft stools. There was a significant treatment-related inhibition of most cholinesterase parameters in both sexes at 10, 40, and 80 mg/kg/day dose groups. The decrease in weight in all groups including the controls was indicative of stress due to the treatment procedure used (i.e., occlusive wraps). For systemic toxicity, the NOAEL was <1 mg/kg/day; a LOAEL was not established. For ChEI, the NOAEL was 1 mg/kg/day and the LOAEL was 10 mg/kg/day based on inhibition of plasma, RBC, and brain cholinesterase activity. This study is classified as supplementary since the protocol (occlusive conditions) did not follow the OPPTS Series 870 Guidelines (non-occlusive conditions) for this type of study (MRID 40079806).

In another dermal toxicity study, groups of New Zealand rabbits (5/sex/dose) received repeated dermal applications of methidathion (technical) in polyethylene glycols 300 at dose levels of 0, 1, 5, or 20 mg/kg/day, six hours per day, five days per week for 21 days. The test material was applied (3mL/kg) to the skin and then covered with a gauze dressing and fastened with adhesive tape (non-occlusive conditions). Controls received the vehicle and the same dressing without the test compound. No treatment-related mortality was seen. Dermal irritation was characterized by papular rash observed in one male at the low, mid, and high dose groups and in two females one at the mid-dose and one at the high-dose. At 20 mg/kg/day, signs of systemic toxicity were limited to hypoactivity in one male during days six to 19. There was a non-statistical decrease in body weight (5%) and body weight gain (18%) in males at 20 mg/kg/day; these were not considered to be adverse effects. No biologically or statistically-significant ChEI was seen at any dose level. No treatment-related histopathological lesions were seen. For systemic

toxicity, the NOAEL was 20 mg/kg/day (HDT); a LOAEL was not established (MRID 40079804).

3. Chronic Toxicity

In a chronic toxicity study, groups of Beagles (4/sex/dose) received diets containing methidathion (technical, 96%) at dose levels of 0, 0.5, 2.0, 4.0, 40 or 140 ppm for 52 weeks. These concentrations were equivalent to 0, 0.02, 0.07, 0.15, 1.33, and 4.51 mg/kg/day, respectively. Treatment had no adverse effect on survival, body weight, body weight gain. Clinical signs of toxicity included salivation, diarrhea, and dacryorrhea (excessive production of tears), but none of the signs showed a dose-response relationship. Food consumption was lower for males at the high dose; however, feed efficiency was not adversely affected when compared to controls. No alterations were seen in plasma cholinesterase activity throughout the study. Red blood cell cholinesterase activity was inhibited in males at 40 ppm (26 to 30%), and 140 ppm (77 to 87%) and in females at 140 ppm (76 to 83%). Brain cholinesterase activity was inhibited in both sexes at 140 ppm (17 to 27%). Statistical significance was reached for both red blood and brain ChEI at 140 ppm. At 40 and 140 ppm, liver enzymes were elevated in both sexes to biologically-significant levels for alkaline phosphatase, SGPT, SGOT, and sorbitol dehydrogenase. Bilirubin was also slightly increased. In females at these doses (40 and 140 ppm), increases in gamma glutamyl transferase were seen along with decreases in total protein and serum albumin. The elevations in hepatic enzymes and serum bilirubin are indicative of hepatocellular damage with accompanying cholestasis. The decrease in total protein and serum albumin in females are also indicative of liver disease. Histopathology revealed cholestasis, characterized by the presence of bile plugs and distended bile canaliculi observed in the centrilobular zone of the livers in dogs at 40 and 140 ppm dose groups. For chronic toxicity, the NOAEL was 0.15 mg/kg/day and the LOAEL was 1.33 mg/kg/day based on red blood ChEI in males as well as elevation of hepatic enzymes and associated hepatic lesions (MRID 41945001).

4. Carcinogenicity

In a chronic toxicity/carcinogenicity study groups of Sprague Dawley rats (50/sex/dose) were fed diets containing methidathion (technical, 97.3%) at dose levels of 0, 4, 40 or 100 ppm for two years. These dose levels corresponded to 0, 0.16, 1.72 or 4.91 mg/kg/day for males and 0, 0.22, 2.20, or 6.93 mg/kg/day for females. There were no treatment-related effects on survival, ophthalmology, hematology or urinalysis parameters, or organ weights. Clinical signs at the mid-and high-dose groups included alopecia, chromorhinorrhea, and several neurological signs such as hypersensitivity to touch, fasciculation, and tremors. Body weight decreases was seen in both sexes of rats at the high dose throughout the study. Food consumption was slightly and minimally increased in males and females, respectively. Water consumption was decreased in females at the high dose; no such effect was seen in males. Inhibition of plasma, RBC and brain cholinesterase activity was seen in both sexes of rats at 40 and 40 ppm dose groups. Treatment-related non-neoplastic lesions were limited to inflammatory and ulcerated lesions of the skin and accumulations of foamy macrophages in the lungs in both sexes of rats at the high dose. **There was no evidence of carcinogenicity in either sex.** For chronic toxicity, the NOAEL was 0.2 mg/kg/day and the LOAEL was 2 mg/kg/day based on plasma, RBC and brain cholinesterase activity (MRID 00160260).

In a carcinogenicity study, groups of CD-1 mice (50/sex/dose) were given methidathion (technical) in their diet at dose level of 0, 3, 10, 50 or 100 ppm (equivalent to 0, 0.46, 1.6, 7.5 or 16.1 mg/kg/day, respectively) for 20 months. Male mice at the high dose (100 ppm) exhibited a decrease in survival primarily during the last 10 weeks of the study. Clinical sign of toxicity was limited to change in the color of urine (dark yellow, orange or red) of male mice at 50 and 100 ppm; no such change in urine color was seen in females. No treatment-related effects were seen in body weight, body weight gain, food consumption, feed efficiency, hematology, or clinical chemistry parameters in either sex at any dose level. Plasma cholinesterase activity was significantly increased (54% over control) in males at 100 ppm. Red blood cell cholinesterase activity was significantly inhibited (30 to 45%) in males at 100 ppm and in females at 50 ppm and 100 ppm, at most time periods. Brain cholinesterase activity was significantly decreased (22 to 49%) in males and females at 100 ppm. Organ weight data showed increases in both absolute and relative liver weights in male mice at 50 and 100 ppm. Treatment-related non-neoplastic lesions in males at 50 and 100 ppm manifested as hepatic

and biliary changes that included bile duct epithelial hyperplasia, biliary stasis, cholangiofibrosis, gall bladder hyperplasia, chronic hepatitis, and cholecystitis. **There was evidence of carcinogenicity only in males at 100 ppm (16.1 mg/kg/day).** At this dose, statistically-significant increase in the incidences of adenomas, carcinomas or combined adenomas plus carcinomas of the liver was seen when compared to controls. For chronic toxicity, the NOAEL was 1.6 mg/kg/day and the LOAEL was 7.5 mg/kg/day based on inhibition of RBC cholinesterase activity (females), increases in absolute and relative liver weights (males), and non-neoplastic lesions (males) (MRID 00157457).

5. Developmental Toxicity

In a developmental toxicity study pregnant Crl:CD(SD) BR rats received oral doses of methidathion (technical, 94.1 to 95.9%) in 3% corn starch at 0, 0.25, 1.0, or 2.25 mg/kg/day during gestation days six through 15. For maternal toxicity, the NOAEL was 1.0 mg/kg/day and the LOAEL was 2.25 mg/kg/day based on one death, decreases in body weight gain and food consumption, cholinergic signs indicative of ChEI, exophthalmia, raspy respiration, and vaginal bleeding. For developmental toxicity, the NOAEL was 2.25 mg/kg/day (HDT); a LOAEL was not established (MRID 40079807).

In a developmental toxicity study, pregnant New Zealand White rabbits were given oral doses of methidathion at 0, 2, 6, or 12 mg/kg/day during gestation day seven through 19. For maternal toxicity, the NOAEL was 6 mg/kg/day and the LOAEL was 12 mg/kg/day based on clinical signs indicative of cholinergic activity. For developmental toxicity, the NOAEL was 12 mg/kg/day (HDT); a LOAEL was not established (MRID's 40079809 and 40079810).

6. Reproductive Toxicity

In a one-generation reproduction study, Sprague-Dawley rats were fed diets containing methidathion at 0, 5, 50, or 100 ppm (reduced to 25 ppm at weaning of F_{1a} litters) for one generation. These doses were equivalent to 0, 0.25, 2.5, or 5 (1.25) mg/kg/day. The parental/systemic NOAEL was 0.25 mg/kg/day and the LOAEL was 2.5 mg/kg/day based on tremors and decreased food consumption during lactation. For offspring toxicity, the NOAEL was 0.25 mg/kg/day and the LOAEL was 2.5 mg/kg/day based on decreased pup birth weight and pup weight during lactation.

In a two-generation reproduction study, Sprague-Dawley rats were fed diets containing methidathion at 0, 5, 25, or 50 ppm (0, 0.25, 1.25, or 2.5 mg/kg/day) for two successive generations. There was no increased sensitivity of pups over the adults. The parental/systemic NOAEL was 0.25 mg/kg/day and the LOAEL was 1.25 mg/kg/day based on tremors and decreased food consumption during lactation and decreased ovarian weight. For reproductive toxicity, the NOAEL was 0.25 mg/kg/day and the LOAEL was 1.25 mg/kg/day based on decreased pup weight and an increased incidence of hypothermia with the appearance of starvation (MRID 40079811-3).

7. Mutagenicity

In a point mutation assay in *Salmonella typhimurium*, methidathion was non-mutagenic without metabolic activation when tested at levels of 25 to 5,000 µg/plate (MRID's: 0078329, 0078330 and 0084010).

In a point mutation study conducted with mouse lymphoma cells that had been exposed to methidathion at doses of 15 mg/kg, only, there was no increase in mutation frequency for resistance to arabinoside or thymidine (Accession #0070213, MRID 0078332).

In a sister chromatid exchange assay, methidathion at doses ranging from 17 to 68 mg/kg produced only a marginal response at the 34 mg/kg dose level. The biological significance of this finding was questionable due to the absence of a dose response relationship (MRID 0078335).

In a Chinese hamster bone marrow assay, methidathion, when administered at doses of 17 to 68 mg/kg, did not increase the percentage of nuclear anomalies (MRID 0078334).

8. Neurotoxicity

In an acute neurotoxicity study, Sprague-Dawley rats were given a single oral (gavage) dose of methidathion at 0, 1, 4, 8 or 15 mg/kg. For neurotoxicity, the NOAEL was 4 mg/kg and the LOAEL was 8 mg/kg based on decreased maze activity and differences in FOB parameters including tremors, bizarre behavior, abnormal gait, ataxia, low arousal, decrease in forelimb grip strength, and uncoordinated righting reflex. For ChEI, the NOAEL was <1 mg/kg (MRID's 43145903 and 43590304).

In a subchronic neurotoxicity study, Sprague-Dawley rats were fed diets containing methidathion (technical, 94.9%) at 0, 3, 10, 30 or 100 ppm (0.2, 0.6, 1.9, or 6.3 mg/kg/day in males and 0.2, 0.7, 2, or 7.2 mg/kg/day, in males and females, respectively) for 90 days. The NOAEL was 3 ppm (0.2 mg/kg/day) and the LOAEL was 10 ppm (0.6 mg/kg/day) based on statistically and biologically-significant decreases in serum, RBC, and brain cholinesterase activity. At 30 ppm, there was also a decrease in RBC and regional central nervous system cholinesterase activity in both sexes. At 100 ppm both sexes showed inhibition of serum, RBC, and brain cholinesterase activity and also females exhibited effects on the Functional Observation Battery that included decreased grip strength, tremors, compulsive sniffing and hyper-responsive behavior (MRID 43582501).

9. Metabolism

In a metabolism study conducted in CD rats, C⁻¹⁴ labeled methidathion was administered at single and preconditioned doses of 0.3 or 3.0 mg/kg. The compound was metabolized and excreted within 24 hours in both sexes, with the primary route of elimination being via the urine. The half-life for elimination was approximately eight hours. The major metabolites that were detected in this study were the organic soluble sulfides, sulfoxide, and sulfone derivatives. Water soluble urinary metabolites included a cysteine conjugate and desmonomethyl methidathion (MRID 40127818).

10. Dermal Absorption

The database does not contain dermal absorption studies.

III. DOSE-RESPONSE ASSESSMENT

A. Special Sensitivity to Infants and Children

On August 8, 1998, the HED FQPA Safety Factor Committee evaluated both the hazard and exposure databases and recommended that the 10x FQPA Safety Factor for methidathion could be reduced to 1x based on the following weight-of evidence:

- (a) The toxicology database is complete to assess susceptibility to infants and children;
- (b) In prenatal developmental toxicity studies, there was no evidence of increased susceptibility in rat or rabbit fetuses following *in utero* exposure since no developmental toxicity was seen at the HDT in either species;
- (c) In the pre/post-natal one generation as well as a two-generation reproduction studies in rats, there was no evidence of increased susceptibility in the pups when compared to parental animals;
- (d) There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post-natal studies. Neither brain weight nor histopathology of the nervous system was affected in the acute, subchronic and chronic toxicity studies in rats and dogs;
- (e) There was no evidence for requiring a developmental neurotoxicity study in rats;
- (f) Adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess dietary (food) exposure and to provide screening level drinking water exposure assessment; and
- (g) There are no registered residential uses at the present time.

B. Toxicology Endpoint Selection

Provided below are the toxicity endpoints used for the methidathion risk assessments. They are summarized in Table 2.

1. Acute Dietary (Acute RfD)

An acute RfD was derived from a NOAEL of 0.2 mg/kg/day and a UF of 100 which includes the 10x interspecies extrapolation and the 10x intraspecies variation factors. The NOAEL was established in a subchronic neurotoxicity study in rats, based on plasma, RBC and brain ChEI at 0.6 mg/kg/day. The acute neurotoxicity study was not selected for this risk assessment, since a NOAEL was not established in that study. However, the NOAEL of 0.2 mg/kg/day selected for the acute RfD is supported by the LOAEL of 1.0 mg/kg/day established in the acute neurotoxicity study based on 41% inhibition of brain (cortex) cholinesterase activity. Application of a 3x UF to the LOAEL of 1 mg/kg/day yields a dose of 0.3 mg/kg/day, which is comparable to the dose (0.2 mg/kg/day) used for deriving the acute RfD.

$$\text{Acute RfD} = \frac{0.2 \text{ mg / kg / day (NOAEL)}}{100 \text{ (UF)}} = \mathbf{0.002 \text{ mg / kg}}$$

As per current OPP policy, an RfD modified by an FQPA Safety Factor is referred to a PAD. Since the FQPA Safety Factor has been reduced to 1x for methidathion risk assessment, the acute RfD is numerically equivalent to the acute PAD. Therefore,
Acute PAD = 0.002 mg/kg.

2. Chronic Dietary (Chronic RfD)

The chronic RfD was derived from a NOAEL of 0.15 mg/kg/day and a UF of 100 which includes the 10x interspecies extrapolation and the 10x intraspecies variation factors. The NOAEL was established in a chronic neurotoxicity study in dogs, based on RBC ChEI and hepatic toxicity at 1.33 mg/kg/day.

$$\text{Chronic RfD} = \frac{0.15 \text{ mg / kg / day (NOAEL)}}{100 \text{ (UF)}} = \mathbf{0.0015 \text{ mg / kg}}$$

As per current OPP policy, an RfD modified by an FQPA Safety Factor is referred to a PAD. Since the FQPA Safety Factor has been reduced to 1x for methidathion risk assessment, the chronic RfD is numerically equivalent to the chronic PAD. Therefore,
Acute PAD = 0.0015 mg/kg.

3. Carcinogenicity Classification

The HED CPRC has classified methidathion as a Group C Carcinogen (possible human carcinogen) based on the increased incidence of liver tumors (adenomas, carcinomas and combined adenomas plus carcinomas) in male mice. The CPRC concluded that a quantitative cancer risk assessment is not required because the evidence as a whole (i.e., common tumor type occurring in one sex, one species, with no increase in proportion of malignant tumor, or apparent shortening of time to tumor) is not strong enough to warrant a quantitative estimation of human risk. This approach is supported by the fact that methidathion is non-mutagenic both *in vivo* and *in vitro*.

4. Occupational Exposure

a. Dermal Absorption

The comparison of the results from the oral and dermal studies yielded conflicting data. In the oral developmental toxicity study in rabbits, the LOAEL was 12 mg/kg/day, the HDT, based on cholinergic signs. Dermal studies in rabbits produced conflicting results: one study (1987) in which the exposure was to the occluded skin, the LOAEL was 1 mg/kg/day based on mortality and ChEI; whereas, in another study (1986) in which exposure was to non-occlusive skin, the LOAEL was 20 mg/kg/day based on decreases in body weight gain and hypoactivity in one male. Comparison of the Acute Oral LD₅₀ (46 mg/kg) and Dermal LD₅₀ (1663 mg/kg) values in rats indicates dermal absorption to be approximately 3%. Comparison of the Acute Oral LD₅₀ (80 mg/kg) and Dermal LD₅₀ (640 mg/kg) values in rabbits indicates dermal absorption to be approximately 13%.

On February 23, 1999, the Hazard Identification Assessment Review Committee (HIARC) evaluated the results of the two 21-day dermal toxicity studies and discounted the 1987 study because the exposure was to the occluded skin which resulted in mortality at the lowest dose tested due to stress from the treatment procedures. The Committee determined that the 1986 study (non-occluded) is appropriate for use in estimating a dermal absorption factor. The Committee concluded that a dermal absorption value can be obtained based upon the reevaluation of the oral and dermal data associated with the rabbit developmental study and the 21-day dermal toxicity study in rabbits. Based on the ratio of the LOAEL of 12 mg/kg/day in the oral developmental toxicity study and the LOAEL of 20 mg/kg/day in the 21-day dermal toxicity study in rabbits, the HIARC extrapolated a 60% dermal absorption factor.

On October 28, 1999, the HIARC, re-evaluated the results of the 1987 twenty-one day dermal toxicity and determined that the NOAEL should be revised to 20 mg/kg/day, based on lack of ChEI as well as statistically or biologically-significant decreases in body weight or body weight gain at this dose (HDT). Revision of this dose from a LOAEL to a NOAEL also required a re-evaluation of the dermal absorption factor since the 20 mg/kg/day dose was previously used to obtain a dermal absorption factor.

The HIARC determined that the ratio of the NOAELs of 6 mg/kg/day in the oral developmental toxicity study in rabbits and the NOAEL of 20 mg/kg/day in the 21-day dermal toxicity study in rabbits yielded a 30% dermal absorption factor. Although 30% may be somewhat of an overestimate of dermal absorption for the technical product, the physical/chemical properties of the technical (i.e., low melting point and good water solubility) would argue for moderate dermal absorption. It should be noted that the EC formulation is severely irritating to the skin which would greatly enhance absorption.

The HIARC also revised the doses and endpoints for dermal risk assessments based on the use pattern, activities and the exposure pattern. Methidathion is applied as the wettable powder formulation to citrus at a maximum rate of 5 lb ai/acre for two applications or the liquid formulation to cotton at a maximum rate of 1 lb ai/acre for two applications. Based on this use pattern, the Committee determined that dermal exposure of only up to 30 days are anticipated for pesticide handlers involved in mixing, loading, and applying methidathion. However, the potential dermal exposures for postapplication activities (such as hoeing, harvesting, and packing) are anticipated to last for several months (i.e., greater than 30 days). No long-term dermal or inhalation exposures are anticipated for handlers or for workers during postapplication activities.

b. Short-Term Dermal

The dermal NOAEL of 20 mg/kg/day established in the 21-day dermal toxicity study in rabbits, based on lack of systemic or dermal toxicity at the highest dose. An MOE greater than 100 does not exceed HED's level of concern for this risk assessment.

c. Intermediate-Term Dermal

An oral NOAEL of 0.2 mg/kg/day, established in the subchronic neurotoxicity toxicity study in rats based on inhibition of plasma, RBC and brain cholinesterase activity at 0.6 mg/kg/day, was selected for this exposure scenario.

The HIARC determined that while the NOAEL of 20 mg/kg/day is appropriate for assessing risks for handlers, since the route (dermal) and the duration (21-days) of exposure is appropriate for the handler exposure period (up to 30 days) of concern, the NOAEL from the 21-day study is not appropriate for assessing the potential postapplication exposure risk. Therefore, the HIARC selected the oral NOAEL of 0.2 mg/kg/day established in the subchronic rat study as appropriate, because: (1) the principal toxicological endpoint (ChEI) was observed following a longer exposure (90 days) in this study (no ChEI was seen in the dermal study); (2) the NOAELs in the two-year chronic toxicity (0.2 mg/kg/day) and the two generation reproduction studies in rats (0.25 mg/kg/day) are comparable to the NOAEL of 0.2 mg/kg/day

in the subchronic study; (3) exposures of 30 days or more are considered highly likely for postapplication activities; and (4) in the absence of a longer-duration dermal toxicity study, the lower NOAEL is used to be protective of workers' health.

Since an oral NOAEL was selected, a dermal absorption factor of 30% should be used for route to route extrapolation. An MOE greater than 100 does not exceed HED's level of concern for this risk assessment.

d. Short and Intermediate-Term Inhalation Exposure

There are only acute inhalation toxicity studies with two formulated products, (22.6% methidathion, $LC_{50} (F) = 0.167 \text{ mg/L}$ and 25% methidathion, $LC_{50} (F) = 0.11 \text{ mg/L}$). Therefore, the HIARC selected the oral NOAEL of 0.2 mg/kg/day established in the 90-day neurotoxicity study in rats. Since an oral value was selected it should be adjusted for 100% inhalation absorption (default value) prior to calculation of the MOE's for short-and intermediate-term exposures. An MOE greater than 100 does not exceed HED's level of concern for this risk assessment.

e. Long-Term Dermal and Inhalation Exposure

The current use pattern (one to two applications/year) does not indicate a concern for potential long-term dermal or inhalation exposures; therefore, risk assessments were not conducted for these pathways.

Table 2. Summary of Toxicology Endpoints Selected for Dietary and Occupational Exposure Risk Assessments

Exposure Period	Dose Selected
Acute Dietary	NOAEL = 0.2 mg/kg/day; UF = 100; RBC 1 Acute RfD = 0.002 mg/kg/day Acute PAD = 0.002 mg/kg/day
Chronic Dietary	NOAEL = 0.15 mg/kg/day; UF = 100; RBC 1 Chronic RfD = 0.0015 mg/kg/day Chronic PAD = 0.0015 mg/kg/day
Cancer	Not Required
Dermal Absorption	30% estimated
Short-Term Dermal	Dermal NOAEL = 20 mg/kg/day MOE =100
Intermediate-Term Dermal	Oral NOAEL = 0.2 mg/kg/day MOE =100
Long-Term Dermal	NOAEL = 0.15 mg/kg/day MOE =100
Short- Intermediate- and Long-Term (Inhalation)	Oral NOAEL = 0.2 mg/kg/day MOE =100

IV. DIETARY EXPOSURE AND RISK CHARACTERIZATION

A. Registered Uses

Methidathion is registered for use on a variety of food/feed crops that include alfalfa (grown for seed) almonds, apples, apricots, artichoke, carambola, cherries, clover (grown for seed), cotton, grapefruit, haygrass, kiwi fruit, lemons, longan, mandarins, mangos, nectarines, olives, oranges, peaches, pears, pecans, plums, prunes, safflower, sugar apple, sunflower, timothy, and walnuts. Methidathion is also used on terrestrial non-food crops such as tobacco and nursery stock. The target pests for methidathion include peach twig borer, scale insects, artichoke plume moth, leafminers, spider mites, boll weevil, bollworms, lygus bug, pink bollworm, whiteflies, aphids, pear psylla, mealybugs, thrips, sunflower stem weevil, sunflower moth, sunflower seed weevils, sunflower midge, Banks grass mites, flea beetles, hornworms, tobacco budworm, codling moth, and hickory shuckworms.

One methidathion MUP is registered to Novartis, Inc. and two MUP's are registered to Gowan Company under the PC Code 100301: the 95% technical (T; EPA Reg. No. 100-530 and 10163-245) and the 50% formulation intermediate (FI; EPA Reg. Nos. 10163-237). All three MUPs are subject to a reregistration eligibility decision. There are four methidathion EUP's with food/feed uses registered to Gowan Company and Novartis, Inc. These EUP's are presented below in Table 3.

Table 3. Methidathion Products

EPA Reg. No.	Label Acceptance Date	Formulation Class	Product Name
10163-244 ^a	5/99	25%WP	Supracide 25W
100-754 ^b	5/95	25% WP	Supracide® 25 WP Insecticide-Miticide
10163-236 ^c	3/95	2 lb/gal EC	Supracide® 2E Insecticide-Miticide
10163-238	5/94	2 lb/gal EC	Supracide® Insecticide-Miticide
^a Includes: AZ 99000700, NV99001000; OR99005300; WA99003000; CA82000400; CA90000200			
^b Includes: ID960010, WA94002000, CA77003900, CA97003000, OR96003000 and OR98002100, NV 99000100, NV 99000200, NV 99000300; WA94000200; AZ99000200			
^c Includes FL92000500 and ID93000300			

The two emulsified concentrate (EC) product registrations owned and maintained by Gowan Co. While these products are not marketed or produced at this time, the Agency must consider these formulations as part of the total potential risk from exposure to methidathion.

The following equipment can be used to apply methidathion: fixed-wing aircraft, airblast sprayer, low pressure handwand, backpack sprayer and groundboom sprayer. Application rates for the WP formulations of methidathion range from 0.25 to 5 lbs ai/acre. EC formulation application rates range from 0.5 to 5.0 lbs ai/acre based on the label revisions submitted by Gowan Co., dated 10/28/99. Information concerning the "typical" application rate was derived from the estimates provided by the Biological and Economical Analysis Division (BEAD) and information provided by the Registrant. A summary of the registered food/feed use patterns of methidathion, based on the product labels is provided in **Table 4**:

Table 4. Summary of Registered Food/Feed Use Patterns

Crop	Maximum lb ai/Acre/ Application	Maximum No. of Applications	Typical lb ai/Acre/ Application	Typical No. of Applications
Almonds	3	1	1.3	1
Artichokes	1	8	0.8	2
Citrus	5	2	2.8	1
Cotton	1 ^a	16	0.6	2
Nursery Stock	0.5	1	0.5 ^b	1
Olives	3	1	2.8	1
Pome fruits	3	1	1.5	1
Stone fruits	3	1	2.0	1
Safflower	0.5	3	1.0	1
Pecans	4	2	1.7	1
Walnuts	3	3	1.3	1
^a Not to exceed 4 lbs ai/acre during any one growing season.				
^b Nursery stock - 0.5 lb ai/100 gallon of water				

B. Exposure -- Food Sources

Potential exposure to methidathion residues in the diet can occur through food and water sources. Tolerances for methidathion residues are currently expressed in terms of methidathion *per se* in plant commodities [40 CFR §180.298(a and c)] and in terms of the combined residues of methidathion, its oxygen analog, and its sulfoxide and sulfone metabolites in animals [40 CFR §180.298(b)]. Based on the available plant and animal metabolism studies, the HED Metabolism Assessment Review Committee (MARC) determined that the residue of concern is methidathion *per se* in plants and animals. The qualitative nature of the residue in plants is adequately understood based on studies with [C14]methidathion on cotton, tomato, artichokes, and citrus. Adequate goat and poultry metabolism studies are available.

The Agency has determined that methidathion represents a 40 CFR §180.6(a)(3) situation in that there is no reasonable expectation of finite residues in animal commodities. Therefore, tolerances will not be required for residues of methidathion in livestock commodities. A summary of the methidathion tolerance reassessment and recommended modifications in commodity definitions are presented in the Tolerance Assessment section.

Adequate data are available to support the established tolerances for methidathion residues in/on the commodities listed in Table C (Attachment 1) of the aforementioned Residue and Product Chemistry Chapters for this chemical. The established tolerance for residues in/on citrus fruit should be increased from 2 ppm to 4 ppm, as residues of 3.4 and 3.5 ppm have been observed following registered use. The commodity definition for "Nuts" should be amended to reflect the correct crop group designation "Tree nuts," and the tolerances for pecans and walnuts, which are covered by the tree nuts group, should be deleted. The tolerance for "Peaches" is not necessary as peaches are covered by the tolerance for residues in/on "Fruits, stone;" therefore HED recommends revocation of the tolerance for peaches. The group definitions "Fruits, pome" and "Fruits, stone" should be revised to "Pome fruits" and "Stone fruits," respectively.

Methidathion residues are generally not expected to occur in any food commodities except citrus. Methidathion is non-systemic and is applied to pome fruits, stone fruits, tree nuts, and some other crops before the edible portion of the plant has formed. Foliar treatments of citrus commodities while the fruit are on the tree do result in residues; however, these residues are almost entirely limited to the peel. Processing of these fruits result in some residues in fruit and

juice at very low levels. USDA PDP data are available for apples, apple juice, oranges, grape fruit, peaches, and canned pears.

Methidathion residue data requirements for cotton gin byproducts which result from changes in the Livestock Feeds Table (TABLE 1, OPPTS Series 860 Test Guidelines; EPA 712-C-96-169, August 1996) should be imposed at this time. However, this requirement should not impinge on the reregistration eligibility decision for methidathion. Field residue data are required on methidathion in the plant byproducts from ginning cotton, consisting of burrs, leaves, stems, lint, and immature seeds. Cotton must be harvested by commercial equipment (stripper and mechanical picker) to provide an adequate representation of plant residue for the ginning process. At least three field trials for each type of harvesting (stripper and picker) are needed, for a total of six field trials. The need for additional tolerances and revisions to the exposure/risk assessments will be made upon receipt and evaluation of required data. When adequate field residue data have been submitted a tolerance must be proposed for this commodity.

The Special Local Need (SLN) label language for use on clover grown for seed contains restrictions to prevent food or feed use of treated plant parts. The registrant has requested to maintain a regional (SLN) registration for the use of methidathion on alfalfa, and timothy hay in Kittitas County, WA. Since 85% of this crop is exported to Japan, and most of the rest is consumed by horses, the potential for dietary intake of methidathion via meat and milk consumption is negligible. However, a regional tolerance under 40 CFR §180.298(c) is required for this use. The general tolerances (40 CFR §180.298(a)) on alfalfa and timothy hay needs to be revoked.

Any additional uses resulting in residues of methidathion in/on livestock feed items may engender the need for tolerances in/on meat, milk, poultry, and eggs.

1. Plant Metabolism

The qualitative nature of the residue in plants is adequately understood based on studies with [¹⁴C]methidathion on cotton, tomato, artichokes, and citrus. Methidathion *per se* is the residue of concern.

2. Animal Metabolism

Adequate goat and poultry metabolism studies are available. Methidathion *per se* is the residue of concern. The Agency has

determined that methidathion represents a 40 CFR §180.6(a)(3) situation in that there is no reasonable expectation of finite residues in animal commodities. Therefore, residues in livestock commodities are not to be regulated.

3. Residue Analytical Methods

Adequate methods are available for data collection and tolerance enforcement pertaining to methidathion *per se* in/on plant commodities. Method I in Pesticide Analytical Manual (PAM), Vol. II is a GLC/flame photometric detection (FPD) method. Methods used for data collection include methods based on the PAM, Vol. II method and other GC methods. There are no requirements for enforcement methodology for animal commodities as the tolerances for animal commodities are to be revoked.

The FDA PESTDATA database dated 1/94 (PAM, Volume I, Appendix I) indicates that methidathion is completely recovered (>80%) by Multiresidue Methods Section 302 (Luke method; Protocol D), exhibited small (<50%) recovery using Methods Section 303 (Mills, Onley, Gaither method; Protocol E, non-fatty), and is completely or partially (50-80%) recovered, depending on the Florisil elution system used, by Multiresidue Method Section 304 (Mills fatty food method; Protocol E, fatty).

4. Storage Stability Data

Storage stability data are available on alfalfa forage, and hay, clover forage, corn forage, corn fodder, corn grain, cottonseed, cottonseed refined oil, kiwifruit, and oranges. However, data are required pertaining to the storage intervals and conditions of crop samples from several studies. The studies lacking storage information are listed in Table 14 of CBRS Nos. 10870 and 11158 (DP Barcodes D184576 and 186643; 3/2/93; R. Perfetti).

5. Magnitude of the Residue in Plants

The reregistration requirements are satisfied for magnitude of the residue in/on, almond hulls, artichokes, carambola, citrus fruits, cottonseed, pome fruits, stone fruits, kiwifruit, longan, mandarins, mangos, nuts, olives, peaches, pecans, safflower seeds, sorghum (fodder, forage, and grain), sugar apple, sunflower seeds, tobacco, and walnuts.

Methidathion residue data requirements for cotton gin byproducts which result from changes in the Livestock Feeds Table should be imposed at this time. However, this requirement should not impinge on the reregistration eligibility decision for methidathion. Data are required on methidathion in the plant byproducts from ginning cotton, consisting of burrs, leaves, stems, lint, and immature seeds. Cotton must be harvested by commercial equipment (stripper and mechanical picker) to provide an adequate representation of plant residue for the ginning process. At least three field trials for each type of harvesting (stripper and picker) are needed, for a total of six field trials. The need for additional tolerances and revisions to the exposure/risk assessments will be made upon receipt and evaluation of required data.

6. Magnitude of the Residue in Processed Food/Feed

Adequate data are available to demonstrate that residues do not concentrate in commodities derived from sunflower seed and these data can be translated to safflower seed. Owing to the use patterns for apples, plums, and olives, finite residues are not expected in the raw agricultural commodities (RAC's) and requirements for processing studies have been waived. Residues concentrate in citrus oil. Based on a highest average field trial (HAFT) residue value of 3.5 ppm for oranges and an average concentration factor of 118x from 10 processing studies, residues of 412 ppm could be expected in citrus oil. Therefore, a tolerance of 420 ppm is appropriate for citrus oil.

Seven processing studies on cottonseed indicate an average concentration factor of 1.9x in cottonseed hulls. The highest average field trial (HAFT) residue for cottonseed is <0.01; therefore, residues in cottonseed hulls would not be expected to exceed the established tolerance of 0.2 ppm on the RAC. A tolerance is not required for cottonseed hulls.

The seven cottonseed processing studies indicate a 1.3x average concentration of residues in refined oil; this does not represent an appreciable concentration. Furthermore, the most recent processing study demonstrated that bleaching refined oil decreased the residues to a level below that in seed and subsequent hydrogenation and deodorization reduced refined oil residues to below the limit of quantitation (<0.05 ppm). A tolerance is not required for refined cottonseed oil.

7. Magnitude of the Residue in Meat, Milk, Poultry, and Eggs

The HED Metabolism Committee has determined that methidathion represents a 40 CFR §180.6(a)(3) situation in that there is no reasonable expectation of finite residues in animal commodities; therefore, livestock feeding studies and tolerances on livestock commodities are not required. Any additional uses resulting in residues of methidathion in/on livestock feed items may engender the need for tolerances in/on meat, milk, poultry, and eggs.

8. Rotational Crops

The available confined rotational crop study is adequate. Field rotational crop data and tolerances for rotated crops are not required.

C. Dietary Risk Characterization – Food Sources

1. Acute Dietary Risk Estimates

An acute dietary probabilistic exposure analysis (Monte Carlo) was conducted for methidathion. This analysis utilized percent crop treated data obtained from a February 20, 1996 BEAD Quantitative Usage Assessment (QUA) and a BEAD QUA from October 27, 1999, which concurs with results of the 1996 QUA. Residue distributions were estimated for food crops based on field trial or PDP monitoring data. Consumption data from the USDA Continuing Surveys of Food Intake by Individuals (CSFII) conducted from 1989 through 1992 was used. This acute dietary risk assessment has been refined (Tier 3), but could be refined even further. The results of the acute analysis are presented in **Table 5**. Because acute dietary risk estimates do not exceed the Agency's level of concern, additional refinement will not be conducted at this time. However, at the time of cumulative risk assessment, additional refinement may be performed.

Most of the residue values entered in the current analysis are estimates based in non-detectable residues in field trials conducted at the maximum use rate. According to current guidance, it would be acceptable to assume that residues are present in these commodities at a level of $\frac{1}{2}$ the limit of detection (LOD); however, in the analysis used for the purposes of this document, the more conservative estimate of $\frac{1}{2}$ the limit of quantification was used. This was done because the basis for determination of an LOD was not obvious. In the case of oranges and grapefruit commodities, an even more conservative approach was taken

for residue below the LOQ. In these cases it was assumed that maximal residues could occur at the level of the LOQ. This was done because of the potential for contamination of pulp and juice during peeling and the appearance of some detectable residues in fruits analyzed in the PDP program. The maximum residue reported for oranges and grapefruit are 0.034 ppm 0.014 ppm.

As per current OPP policy, an RfD modified by an FQPA safety factor is referred to as a PAD. Since the FQPA Safety Factor Committee determined that the 10x FQPA safety factor should be reduced to 1x for the methidathion risk assessment, the RfD is equal to the PAD.

Table 5. Acute Dietary (Food) Exposure and Risk Estimates

Acute Dietary Risk (Food Only)						
Population	95 th percentile		99 th percentile		99.9 th percentile	
	Exposure (mg/kg/day)	% of Acute PAD	Exposure (mg/kg/day)	% of Acute PAD	Exposure (mg/kg/day)	% of Acute PAD
U.S. Population	0.000041	2.1	0.000112	5.6	0.000318	15.9
Females (13+)	0.000051	2.6	0.000123	6.2	0.000281	14.1
Children (1-6 years)	0.000105	5.3	0.000252	12.6	0.000558	27.9
Nursing infants <1yr	0.000032	1.6	0.000246	12.3	0.001280	64.0

This highly refined risk assessment based on an acute PAD of 0.002 mg/kg/day and conducted at 99.9th percentile exposure, reveal that the **acute dietary risk posed by methidathion does not exceed HED's level of concern**; the percentage of the acute PAD occupied ranged from 14% for females (13+ years old) to 64% for nursing infants (<1 year old).

2. Chronic Dietary Risk Estimates

A Tier 2 chronic dietary risk assessment for methidathion was conducted using the Dietary Risk Estimate System (DRES) analysis, incorporating percent crop treated data and some anticipated residue data, and the chronic PAD of 0.0015 mg/kg/day. These results are summarized in **Table 6**. Additional refinements could be made resulting in lower chronic dietary exposure estimates.

Table 6. Chronic Dietary (Food) Exposure and Risk Estimates

Chronic Dietary Risk (Food Only)		
Population	Exposure (mg/kg/day)	% Chronic PAD
U.S. Population	0.000137	9
Females (13+)	0.000040	3
Children (1-6 years)	0.000338	23
Non-nursing infants <1 yr	0.000179	12

Based on the estimated exposure and percent chronic RfD values, **the chronic dietary risk posed by methidathion does not exceed HED's level of concern.** The percentage of the chronic PAD occupied ranged from 3% for females (13 +, nursing) to 23% for children (1-6 years of age).

HED's CPRC classified methidathion as a Group C carcinogen and determined that a quantitative cancer risk assessment was not required since the evidence for carcinogenicity as a whole was not robust enough to warrant a quantitative estimation of human risk. In the case of methidathion, cancer risk from dietary exposure is less of a concern because: (1) while the chronic NOAEL was 0.15 mg/kg/day for RBC ChEI, tumors were seen in mice only at the HDT (16 mg/kg/day) in the presence of significant RBC (30 to 45% inhibition) and brain (22 to 49%) ChEI in both sexes; (2) the dose of 0.15 mg/kg/day used for deriving the chronic RfD is approximately 107-fold lower than the dose (16 mg/kg/day) that caused tumors; (3) the primary concern is the non-cancer risk which manifests as ChEI at a very low dose (1.3 mg/kg/day); (4) the application of the 100 UF to the chronic NOAEL yields a chronic RfD that provides even more protection for non-dietary cancer dietary risk (i.e., the chronic RfD of 0.0015 mg/kg/day is approximately 11,000 times lower than the dose at which tumors were seen); and (5) the evidence for carcinogenicity was limited to the presence of a common tumor type (liver tumors) occurring in one sex (males), in one species (mice) with no increase in proportion of malignant tumors or apparent decrease in the latency period.

D. Drinking Water Sources

The EFED estimated EECs for methidathion in memorandums dated December 17, 1997 and December 30, 1998.

1. Ground Water

EFED conducted Tier I, *SCI-GROW* (Screening Concentration in Groundwater) modeling to estimate methidathion concentrations in groundwater based on application rates of the pesticide. The *SCI-GROW* modeling results provided HED an upper-bound EEC of 0.4 ppb methidathion in groundwater.

2. Surface Water

EFED conducted refined Tier II, *PRIZM-EXAMS* modeling to determine peak and chronic methidathion EECs based on refined usage data and meteorological information. According to EFED modeling estimates, the peak and 56-day average concentrations of methidathion in surface waters, are 5.6 ppb and 0.6 ppb respectively.

3. Drinking Water - Monitoring Data

In addition to the modeling estimates provided above, EFED also evaluated results of available monitoring data from 264 drinking water sources from California, (259 from groundwater). The monitoring data suggests drinking water concentrations of methidathion will not exceed 5 ppb. Based on the available information, EFED concludes that monitoring and modeling data suggest drinking water concentrations of methidathion will not exceed 6 ppb.

E. Dietary Risk Characterization – Drinking Water Sources

1. Drinking Water Levels of Comparison

Currently, HED uses DWLOCs as a surrogate to capture risk associated with exposure to pesticides in drinking water. A DWLOC is the concentration of a pesticide in drinking water that would be acceptable as an upper limit in light of total aggregate exposure to that pesticide from food, water, and residential uses (if any). A DWLOC may vary with drinking water consumption patterns and body weights for specific subpopulations.

Based on the acute and chronic dietary exposure estimates presented in Tables 5 and 6, DWLOCs were calculated using the formulae listed below. A human health DWLOC is the concentration of a pesticide in drinking water which would result in unacceptable aggregate risk, after having already factored in all food exposures and other non-occupational exposures for which OPP has reliable data.

$$DWLOC_{acute} = \frac{[acute\ water\ exposure\ (mg/kg/day) \times (body\ weight)]}{[consumption\ (L) \times 10^{-3}\ mg/\mu g]}$$

where:

$$acute\ water\ exposure\ (mg/kg/day) = aRfD - acute\ food\ exposure\ (mg/kg/day)$$

$$DWLOC_{chronic} = \frac{[chronic\ water\ exposure\ (mg/kg/day) \times (body\ weight)]}{[consumption\ (L) \times 10^{-3}\ mg/\mu g]}$$

where:

$$chronic\ water\ exposure\ (mg/kg/day) = [RfD - (chronic\ food\ exposure)\ (mg/kg/day)]$$

The Agency's default body weights and consumption values used to calculate DWLOCs are as follows: 70 kg/2L (adult male); 60kg/2L (adult females) and 10 kg/1L (child).

Since acute and chronic dietary exposures to pesticidal residues of methidathion do not exceed EPA's levels of concern, EPA used the acute and chronic PADs and the acute and chronic exposure values to calculate the DWLOCs for the U.S. population and the two most sensitive subgroups identified in the dietary exposure assessments for acute and chronic exposures. **Table 7** summarizes the acute DWLOCs and acute model EECs. **Table 8** summarizes the chronic DWLOCs and chronic model EECs.

Table 7. Acute DWLOCs and Acute Model EECs

Population Subgroup	aPAD (mg/kg/day)	Acute Food Exposure (mg/kg/day)	Available Water Exposure (mg/kg/day)	DWLOC _A ^{cute} (ppb)	PRZM-EXAMS Acute EEC (ppb)	SCI-GROW EEC (ppb)
US Population	0.002	0.000318	0.001682	59	6	0.4
Adult Female	0.002	0.000233	0.001767	53	6	0.4
Infants <1 yr	0.002	0.001280	0.000720	7.2	6	0.4
Children 1-6	0.002	0.000558	0.001442	22	6	0.4

Table 8. Chronic DWLOCs and Chronic Model EECs

Population Subgroup	cPAD (mg/kg/day)	Chronic Food Exposure (mg/kg/day)	Available Water Exposure (mg/kg/day)	DWLOC _{Chronic} (ppb)	PRZM-EXAMS Chronic EEC (ppb)	SCI-GROW EEC (ppb)
US Population	0.0015	0.000137	0.001363	48	0.6	0.4
Adult Female	0.0015	0.000040	0.001460	44	0.6	0.4
Infants <1 yr	0.0015	0.000179	0.001321	13	0.6	0.4
Children 1-6	0.0015	0.000338	0.001162	17	0.6	0.4

By comparing the peak methidathion EECs of 6 ppb for surface water and maximum 5.0 ppb for groundwater, based on the monitoring data, to the acute DWLOCs, it is apparent that **the acute DWLOCs are not exceeded for any of the population subgroups.**

Chronic concentrations of methidathion in surface waters and groundwater are expected to be less than 1 ppb, therefore the **chronic DWLOCs are not exceed for any of the population subgroups.**

V. OCCUPATIONAL & RESIDENTIAL EXPOSURE AND RISK CHARACTERIZATION

There are potential occupational exposures to pesticide handlers (mixers/loaders/applicators) and to workers when applying methidathion or during postapplication activities, such as scouting and harvesting. Methidathion is applied as a wettable powder formulation in water soluble packets (WSP) to citrus at a maximum rate of 5 lb ai/acre for two applications per year or to cotton at a maximum rate of 1 lb ai/acre for two applications year. Occupational handlers and workers are potentially exposed via dermal and inhalation routes; however, inhalation exposure during postapplication activities is considered to be minimal for methidathion. Based on the use pattern, dermal exposure of up to 30 days are anticipated for pesticide handlers involved in mixing, loading and applying methidathion. However, based on harvesting and other cultural activities for several crops, postapplication dermal exposures may last up to several months. Representative postapplication activities of concern include: scouting activities associated with cotton in North Carolina, Texas and California; hoeing, irrigation and packing activities associated with artichokes; and harvesting activities associated with citrus, kiwi fruit, longan and carambola. The exposure scenario descriptions for methidathion and standard assumptions that were used are listed in **Table 9**.

There are no registered uses of methidathion in residential settings and none of the registered occupational uses are likely to involve applications to public access areas or at residential sites. There may be potential for spray drift associated with the aerial applications or other high volume spray in densely populated agricultural areas where peripheral residential exposures and/or exposure to farm worker children could occur. An assessment of the potential exposure and risk from spray drift associated with agricultural use of methidathion has not been included in this document. The Agency is in the process of developing guidance and procedures characterizing these kind of exposures. This guidance will be included in our upcoming revised Standard Operating Procedures (SOP's) for Residential Exposure Assessment.

Table 9. Exposure Scenario Descriptions for the Use of Methidathion

Exposure Scenario (Number)	Standard Assumptions (8-hr Work Day)	Comments
Mixer/loader Descriptors		
Mixing/Loading Water Soluble Packets (WSP) (#1a, 1b and 1c)	aerial = 350 acres groundboom = 80 acres airblast = 40 acres	<p>Minimum PPE: "Best Available" grades: Hands= acceptable grades, dermal = acceptable grades, inhalation = all grades. Hands 5 replicates; dermal = 6 to 15 replicates; inhalation = 15 replicates. Low confidence in all data due to insufficient replicates.</p> <p>PPE: "Best Available" grades: Hands, dermal, all grades. Hands 9 replicates; dermal = 6 to 15 replicates. Low confidence in hands and dermal data.</p> <p>PHED data used for minimum PPE, no Protection Factors (PFs) were necessary. A 50% PF was used for PPE to represent double layer of clothing.</p>
Mixing/Loading Liquid Formulations (#2a, 2b and 2c)	aerial = 350 acres groundboom = 80 acres airblast = 40 acres	<p>Minimum PPE: "Best Available" grades: Hands= acceptable grades, dermal = acceptable grades, inhalation =AB grades. Hands 59 replicates; dermal = 72 to 122 replicates; inhalation = 85 replicates. High confidence.</p> <p>PPE: AB grades: Hands 59 replicates; dermal = 73 to 122 replicates; inhalation = 85 replicates. High confidence.</p> <p>PHED data used for minimum PPE, no PF's were necessary. A 50% PF was used for PPE to represent double layer of clothing.</p>
Applicator Descriptors		
Applying Sprays with a Fixed-wing Aircraft (#3)	350 acres.	<p>Engineering Controls: "Best Available" grades: Hands = acceptable grades; dermal, and inhalation ABC grades. Hands = 34 replicates; dermal = 24 to 48 replicates; inhalation = 23 replicates. Medium Confidence in dermal and inhalation data.</p> <p>PHED data used, no PFs were necessary.</p>

Exposure Scenario (Number)	Standard Assumptions (8-hr Work Day)	Comments
Applying Sprays with a Groundboom Sprayer (#4)	80 acres.	<p>Minimum PPE: "Best Available" grades: Hands, dermal, and inhalation acceptable grades. Hands = 21 replicates; dermal = 23 to 42 replicates; inhalation = 22 replicates. High confidence in dermal and inhalation data.</p> <p>PHED data used for minimum PPE. A 50% PF representing coveralls was used for PPE on dermal data.</p> <p>Enclosed cab, Hand=16; Inhalation = 16; Dermal: 20-31</p>
Applying Liquids with an Airblast Sprayer (#5)	40 acres.	<p>Minimum PPE: "Best Available" grades: Hands, dermal, and inhalation = acceptable grades. Hands = 22 replicates; dermal = 32 to 49 replicates; inhalation = 47 replicates. High confidence in dermal and inhalation data.</p> <p>PPE: "Best Available" grades: Hands, dermal, and inhalation = acceptable grades. Hands = 18 replicates; dermal = 31 to 48 replicates; inhalation = 47 replicates. High confidence in dermal and inhalation data.</p> <p>Engineering Controls: "Best Available" grades: Hands, dermal, = acceptable grades, inhalation = grades ABC. Hands = 20 replicates; dermal = 20 to 30 replicates; inhalation = 9 replicates. High confidence in dermal data, low confidence for inhalation data.</p> <p>PHED used for minimum PPE. A 50% PF representing coveralls was used for PPE on dermal data. An 80% PF was used for half-face respirator on inhalation data. Engineering control data were collected wearing gloves (an unusual clothing scenario, but only data available). PHED data used, no PFs necessary.</p>
Mixer/Loader/Applicator Descriptors		
Mixing/Loading/Applying WSP using a Low Pressure Handwand (#6)	10 gallons.	<p>Single Layer, with Gloves</p> <p>Total Deposition: "Best Available" grades: Hands all grades; dermal grades ABC; and inhalation grades ABC. Hands = 15 replicates; dermal = 16 replicates; and inhalation = 16 replicates. Medium confidence in hands, dermal, and inhalation data.</p> <p>Lack of "no glove" hand data.</p>

Exposure Scenario (Number)	Standard Assumptions (8-hr Work Day)	Comments
Mixing/Loading/Applying WSP using a Backpack Sprayer (#7)	40 gallons	<p>Single Layer, No Gloves: "Best Available" grades: Hands and dermal grades AB; Inhalation acceptable grades. Hands = 0 replicates; Dermal = 9 to 11 replicates; Inhalation = 11 replicates. Low confidence in dermal and inhalation data due to inadequate replicate number.</p> <p>Single Layer, Gloves: Hands = 11 replicates, C grade. Dermal = 9 to 11 replicates, AB grade; Inhalation 11 replicates acceptable grade.</p> <p>PHED data used for PPE. No Glove scenario not used due to lack of data.</p>
Flagger Descriptors		
Flagging Aerial Spray Applications (#8)	350 acres.	<p>Minimum PPE: "Best Available" grades: Hands, dermal, and inhalation acceptable grades. Hands = 30 replicates; dermal = 18 to 28 replicates; inhalation = 28 replicates. High confidence in dermal and inhalation data.</p> <p>PPE Glove - Hand = 6, low confidence. A 50% PF was added to dermal data for PPE to represent coveralls. A 90% PF was added to represent gloves. A 98% PF was added for Engineering Controls to represent an enclosed cab.</p>
<p>DATA SOURCE: PHED V1.1</p> <p>^aStandard Assumptions based on an 8-hour work day.</p> <p>^b"Best Available" grades are defined by HED SOP for meeting OPPTS Series 875 Guidelines. Best available grades are assigned as follows: matrices with grades A and B data <u>and</u> a minimum of 15 replicates; if not available, then grades A, B and C data and a minimum of 15 replicates; if not available, then all data regardless of the quality and number of replicates. Data confidence are assigned as follows:</p> <p>High = grades A and B and 15 or more replicates per body part Medium = grades A, B, and C and 15 or more replicates per body part Low = grades A, B, C, D and E <u>or</u> any combination of grades with less than 15 replicates</p>		

On October 28, 1999, the Gowan Company informed the Agency of lower maximum application rates of 0.5 to 5 lb ai/acre (reduced from 10 lbs ai/acre) for the liquid formulation. Consequently, a lower maximum application rate, comparable to the wettable powder formulation of 5 lbs a.i/acre is used in this assessment.

On July 1, 1999, the Gowan Company requested HED to reevaluate the NOAEL/LOAEL established in the 21-day dermal toxicity study and its impact on the doses and endpoint selected for occupational exposure risk assessments. In response to this request, the HIARC evaluated the results of that study and other appropriate toxicology data, specifically with regard to the handler exposure duration and postapplication activities. The HIARC determined that based on one to two applications per year, handler exposures are anticipated not to be more than 30 days, where as postapplication exposure (hoeing, harvesting and packing) are anticipated to last for up to several months. The risk assessment is based on the revised doses and endpoints selected for the appropriate exposure groups (i.e, handlers and postapplication workers).

A. Occupational Handler Exposure Scenarios

HED has identified 12 major exposure scenarios, for which there is potential for occupational handler exposure during mixing, loading and applying products containing methidathion to agricultural crops and to non-agricultural use sites. These occupational scenarios reflect a broad range of application equipment and use sites, and are presumed to have exposure not more than 30 days based primarily on the frequency of the use pattern.

The estimated exposures considered minimum PPE (long pants and a long-sleeved shirt, gloves, and an open cab or tractor), additional PPE (coveralls in addition to the 'minimum PPE,' plus dust/mist respirator), as well as engineering controls (water soluble packets (WSP), closed mixing systems, enclosed cockpit or cabs for applications).

The 12 major handler exposure scenarios identified for methidathion include the following; they are summarized in **Table 10**:

- ◆ Mixing/loading water soluble packets (WSP) in support of aerial, groundboom sprayer, and airblast sprayer application (#1a, 1b and 1c)
- ◆ Mixing/loading liquid formulation in support of aerial, groundboom sprayer, and airblast sprayer application (#2a, 2b and 2c)

- ◆ Liquid aerial application with a fixed-wing aircraft (#3);
- ◆ Liquid groundboom sprayer application (#4);
- ◆ Liquid airblast sprayer application (#5);
- ◆ Liquid mixing/loading/application with a low pressure sprayer (#6);
- ◆ Liquid mixing/loading/application with a backpack sprayer (#7);
and,
- ◆ Flagging of aerial liquid application (#8).

Table 10. Summary of Occupational Exposure Scenarios

Scenario No.	Description	Product Form	Application Method	Crops	Acres Treated
1a, 1b, 2a, 2b,	M/L	WSP/EC	Aerial	Citrus/Cotton	350
1 b and 2b	M/L	WSP/EC	Groundboom	Cotton/Artichoke	80
1c /2c	M/L	WSP/EC	Airblast	Citrus/Apples	40
3	Applicator	Liquid	Aerial	Citrus/Cotton	350
4	Applicator	Liquid	Groundboom	Citrus/Cotton	80
5	Applicator	Liquid	Airblast	Citrus/Apples	40
6	M/L/A	Liquid	Low Pressure Hand Wand	Nursery stock	10 gal ^a
7	M/L/A	Liquid	Backpack Sprayer	Nursery stock	40 gal ^a
8	Flagger	Liquid	Aerial	Citrus	350
M/L/A = Mixer/Loader/Applicator; WSP = Water Soluble Packets; EC= Emulsifiable Concentrate; ^a 0.5 lb ai/100 gallon of water					

B. Occupational Handler Exposure Data Sources and Assumptions

HED does not have chemical specific handler studies for methidathion. Consequently, occupational exposure estimates are based on surrogate data from PHED, Version 1.1. PHED is a software system consisting of two parts--a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions and a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the PHED database contains values for over 1700 monitored individuals (i.e., replicates). Users select criteria to subset the PHED database to reflect the exposure scenario being evaluated. The subsetting algorithms in PHED are based on the central assumptions that the magnitude of handler exposures to pesticides are primarily a function of activity (e.g., mixing/loading, and applying), formulation product type (e.g., wettable powders, granulars), application method (e.g., aerial, groundboom), and clothing scenarios (e.g., gloves, double layer clothing). While data from PHED provides best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pound of active ingredient (a.i.)) may not accurately represent labeled uses in all cases. HED has developed a series of tables of standard unit exposure (UE) values for many occupational exposure scenarios that can be utilized to ensure consistency in exposure assessments.

In addition to the use of standard unit exposure values based on PHED database, the following assumptions and factors were used to complete the exposure assessment for methidathion:

- ◆ Maximum label rates for representative crops.
- ◆ Average body weight of an adult handler is 70 kg.
- ◆ Average work day interval represents an 8-hour workday (e.g., the acres treated or volume of spray solution prepared in a typical day).
- ◆ Daily acres and volumes (as appropriate) to be treated in each scenario include:
 - 350 acres for aerial and chemigation applications (including flaggers supporting aerial applications);
 - 80 acres for groundboom applications;
 - 40 acres for airblast sprayer;
 - 40 gallons for low pressure handwand;
 - 10 gallons for backpack sprayer.

Based on the use pattern and exposure potential the doses and endpoints selected for handler exposure risk assessment are as follows:

- ◆ For handlers (mixer/loader/applicators) **dermal** exposures: Dermal NOAEL of 20 mg/kg/day established in the 21-day dermal toxicity study in rabbits based on lack of systemic toxicity. Since this NOAEL is from a dermal study, a dermal absorption factor is not required for these assessments.
- ◆ For handlers (mixers/loaders/applicators) **inhalation** exposures: Oral NOAEL of 0.2 mg/kg/day established in the subchronic neurotoxicity study in rats based on ChEI due to lack of inhalation toxicity studies; 100% (default value) absorption factor was used in route-to-route extrapolation (i.e., inhalation and oral absorption are equivalent).

Average daily doses (ADD, mg/kg/day) were calculated for dermal and inhalation exposure assessments for handlers (mixer/loader/applicator) as follows:

Dermal ADD = PHED unit exposure (mg/lb ai) x Amount handled (lb a.i handled/day) x Conversion Factor, 1 mg/1,000 µg ÷ Adult Body weight (70 kg). A dermal absorption factor is not required due to the use of a NOAEL from a dermal study.

Inhalation ADD = PHED unit exposure (mg/lb ai) x Amount handled (lb a.i handled/day) x Inhalation Absorption factor (100%, default) Conversion Factor, 1 mg/1,000 µg ÷ Adult Body weight (70 kg).

Because the dermal and inhalation NOAELs are based on different toxicological endpoints (dermal lack of systemic toxicity and ChEI for inhalation), it is inappropriate to add exposures for these pathways. Therefore, only route-specific MOE's are presented in this risk assessment. The MOE's are calculated by comparing the route-specific exposure to appropriate NOAEL. An MOE equal to or greater than 100 does not exceed HED's level of risk concern for pesticide handler exposure to methidathion.

C. Occupational Handler Risk Characterization

MOE's were derived based upon the comparison of dermal exposure estimates (i.e., ADD) against the NOAEL of 20 mg/kg/day for dermal exposure. The inhalation exposure estimates (ADD) are compared against the oral NOAEL of 0.2 mg/kg/day for inhalation exposures. An MOE of 100 does not exceed HED's level of concern. Handler exposure estimates and MOE's are presented in **Table 11** with minimum PPE and gloves and in **Table 12** with additional PPEs and/or engineering controls.

1. Dermal Exposure Risk Characterization

With minimum PPE (single layer clothing and gloves), eight of 12 exposure scenarios result in exposure/risk margins which does not exceed HED's level of concern; (i.e., MOE's are ≥ 100). The remaining four scenarios that are of risk concern (i.e., MOE's less than 100) are:

- ◆ (#1a). Mixing/Loading Water Soluble Packet in support of Aerial Application (MOE=80)
- ◆ (#2a). Mixing/Loading Liquid Formulation in support of Aerial Application (MOE=34)
- ◆ (#5). Airblast Sprayer (MOE = 29)
- ◆ (#8). Flagger- Liquid Application (MOE = 70).

With additional PPE (coveralls over single layer clothing and gloves), risk is mitigated for:

- ◆ (#1a). Mixing/loading WSP in support of aerial application (MOE = 140).

With engineering controls (closed cab and single layer clothing), risk is mitigated for:

- ◆ (#5). Airblast sprayer (MOE = 370).
- ◆ (#8). Flagging of liquid application (MOE = 3,600)

Table 11. Occupational Handler Exposure Estimate and Risk Assessment - Minimum PPE (Single Layer Clothing + Gloves)

Exposure Scenario		Dermal			Inhalation		
		with Minimum PPE ^a			No respirator		
Mix/Loading/Application Scenario	(lb ai/day)*	UE ^b (mg/lb ai)	ADD ^c (mg/kg/day)	MOE ^d	UE ^b (mg/lb ai)	ADD ^c (mg/kg/day)	MOE ^d
Mixing/Loading Exposure Scenario							
Mixing/Loading Water Soluble Packet (WSP) in support of Aerial Application in (#1a)	1750	0.0098	0.25	80	0.00024	0.006	33
Mixing/Loading WSP in support of Powder in support of Groundboom Application (#1b)	80		0.011	1800		0.00028	710
Mixing/Loading WSP in support of Airblast Sprayer Application (#1c)	200		0.028	710		0.00069	290
Mixing/Loading Liquid Formulation in support of Aerial Application (#2a)	1750	0.023	0.58	34	0.0012	0.03	7
Mixing/Loading Liquid Formulation in support of Groundboom Application (#2b)	80		0.026	770		0.0014	150
Mixing/Loading WSP in support of Airblast Sprayer Application (#2c)	200		0.07	290		0.0034	60
Applicator Exposure							
Aerial Application with a Fixed-Wing Aircraft (liquid) (#3)	1750	See Engineering Controls					
Groundboom (#4)	80	0.014	0.016	1250	0.00074	0.0008	250
Airblast Sprayer (#5)	200	0.24	0.68	29	0.0045	0.013	15

Exposure Scenario		Dermal			Inhalation		
		with Minimum PPE ^a			No respirator		
Mix/Loading/Application Scenario	(lb ai/day)*	UE ^b (mg/lb ai)	ADD ^c (mg/kg/day)	MOE ^d	UE ^b (mg/lb ai)	ADD ^c (mg/kg/day)	MOE ^d
Mixer/Loader/Applicator Exposure							
Low Pressure Handwand (liquid) (#6)	0.05	0.43	0.00031	65,000	0.03	0.000021	9300
Backpack Sprayer (liquid) (#7)	0.20	2.5	0.007	2,800	0.33	0.0009	210
Flagger Exposure							
Liquid Application (#8)	1750	0.012	0.3	70	0.00035	0.0088	23
<p>*lb. ai/day = Max. Appl. Rate (lb ai/acre) * Max Area Treated (acres/day) Scenarios: 1a, 2a, 3 and 8 (5lbs ai./acre x 350 acres = 1750 lb a.i./day) Scenarios: 1b, 2b, and 4 (1 lb ai/acre x 80 acres = 80 lb a.i./day) Scenarios: 1c, 2c, and 5 (5 lbs ai/acre x 40 acres = 200 lb a.i./day) Scenarios: 6: 0.5 lb ai/100 gal. at 10 gallons applied for low pressure handwand Scenario 7: 0.5 lb ai/100 gal. at 40 gallons applied for backpack sprayer liquid</p> <p>^aThe minimum PPE is long sleeve shirt, long pants, shoes, socks and gloves</p> <p>^bUnit Exposure (UE) is value from PHED Ver 1.1 Surrogate Exposure Guide (Aug 1998)</p> <p>^cADD=Average Daily Dose (mg/kg/day) = [PHED unit exposure(mg/lb ai) * Amount handled (lb ai handled/day) /70 kg body wt.* 100% inhalation absorption factor; a dermal absorption factor is not required due to the use of a NOAEL from a dermal study.</p> <p>^dMOE=NOAEL/ADD = Dermal = 20.0 mg/kg/day ; Inhalation: oral NOAEL = 0.2 mg/kg/day. An MOE of ≥100 is required.</p>							

Table 12. Occupational Handler Exposure Estimate and Risk Assessment with Protective Equipment and /or Engineering Controls

Exposure Scenario (Up to 30 Days)		Dermal						Inhalation			Inhalation		
		With coveralls ^a			With engineering controls ^b			With Dust/Mist Respirator ^a			With engineering controls		
Mixing/ Loading/ Application	(lb ai/day)	UE ^c (mg /lb ai)	ADD ^d (mg/kg/ day)	MOE ^e	UE ^c (mg/lb ai)	ADD ^d (mg/kg/ day)	MOE ^e	UE ^c (mg/lb ai)	ADD ^d (mg/kg/ day)	MOE ^e	UE ^c (mg/lb ai)	ADD ^d (mg/kg/ day)	MOE ^e
Mixer/Loader Exposure													
Mixing/Loading WSP in support of Aerial Application (1a)	1750	0.0057	0.14	140	NA	NA	NA	4.8 E-5	1.2E-3	170	NA	NA	NA
Mixing/Loading WSP in support of Airblast Sprayer Application (1c)	200	0.0057	0.016	1250	NA	NA	NA	4.8 E-5	1.4E-4	1400	NA	NA	NA
Mixing/Loading Liquid in support of Aerial Application (2a)	1750	0.018	0.45	45	0.0086	0.22	91	2.4 E-4	6.0E-3	33	8.3 E-5	2.1E-3	95
Mixing/Loading Liquid in support of Airblast Application (2c)	200	0.018	0.051	390	NA	NA	NA	2.4 E-4	6.9E-4	290	8.3 E-5	2.4E-4	830
Applicator Exposure													
Aerial Application with a Fixed-Wing Aircraft liquid (3)	1750	SEE ENGINEERING CONTROLS			0.005	0.13	150	SEE ENGINEERING CONTROLS			6.8 E-5	1.7E-3	120
Airblast Sprayer (5)	200	0.22	0.63	32	0.019	0.054	370	9 E-4	2.6E-3	77	4.5 E-4	1.3E-3	153

Exposure Scenario (Up to 30 Days)		Dermal						Inhalation			Inhalation		
		With coveralls ^a			With engineering controls ^b			With Dust/Mist Respirator ^a			With engineering controls		
Mixing/ Loading/ Application	(lb ai/day)	UE ^c (mg /lb ai)	ADD ^d (mg/kg/ day)	MOE ^e	UE ^c (mg/lb ai)	ADD ^d (mg/kg/ day)	MOE ^e	UE ^c (mg/lb ai)	ADD ^d (mg/kg/ day)	MOE ^e	UE ^c (mg/lb ai)	ADD ^d (mg/kg/ day)	MOE ^e
Mixer/Loader/Applicator Exposure													
Flagger Exposure													
Liquid Application (8) ^f	1750	0.011	0.28	71	0.00022	5.5E-3	3600	7 E-5	1.8 E-3	110	7.0 E-6	1.8E-4	1100

Baseline dermal unit exposure represents long pants, long sleeve shirts, open mixing/loading, open cab tractor (open cab tractor does not apply to 6, 7 and 8). Baseline inhalation unit exposure represents no respirator.

^a**Dermal:** The addition of coveralls provides a 50% reduction of dermal exposure to the body (does not include head & neck). Additional PPE dermal unit exposure represents coveralls over single layer of clothing and chemical resistant gloves, open mixing/loading, open cab tractor (open cab tractor does not apply to 6, 7 and 8), except flaggers do not use gloves.

Inhalation: Use of a dust/mist respirator = 80% reduction in exposure.

^b**Engineering Controls:**

Scenarios 1a and 1c: WSP, double layer clothing, and gloves- additional engineering controls not possible since all WP products are only sold as WSP.

Scenarios 2a and 2 c: Closed systems

Scenarios 3: Closed cockpit, single layer clothing (SLC) and no chemical resistant gloves

Scenarios 5: Closed cab, single layer clothing and no chemical resistant gloves.

Scenario 8: Flagger in enclosed cab vehicle with SL clothing.

^cUnit Exposure (UE) is value from the PHED Ver 1.1 Surrogate Exposure Guide (Aug 98).

^dADD(mg/kg/day) = [PHED unit exposure(mg/lb ai) * Amount handled (mg ai handled/day)] /70 kg by wt. times 100% inhalation absorption factor. No dermal absorption factor required since dose selected is from a dermal study.

^eMOE=NOAEL/ADD = Dermal NOAEL = 20.0 mg/kg/day ; Inhalation: oral NOAEL = 0.2 mg/kg/day. A MOE of ≥ 100 is required.

^fFlagger in truck- SLC, no gloves. Truck (engineering control) offers 98% exposure reduction over baseline.

Risk is not mitigated (either with additional PPEs (MOE=91) or with engineering controls) for:

- ◆ (#2a). Mixing/loading liquid formulation in support of aerial application (MOE = 95).

2. Inhalation Exposure Risk Characterization

With minimum PPE (single layer clothing with no respirator), six of 12 scenarios result in exposure/risk margins that do not exceed HED's level of concern. One scenario does not have data for minimum PPE, and the remaining five scenarios (listed below) have risk estimates that exceed HED's level of concern (i.e., MOE's less than 100):

- ◆ (#1a). Mixing/loading WSP in support of aerial application (MOE=33);
- ◆ (#2a). Mixing/loading liquid formulation in support of aerial application (MOE=7);
- ◆ (#2c). Mixing/loading liquid formulation in support of airblast sprayer application (MOE=60)
- ◆ (#5). Airblast Sprayer application (MOE = 15), and
- ◆ (#8). Flagger of aerial liquid application (MOE = 23)

With additional PPE, (coveralls over single layer clothing, gloves, and a dust/mist respirator, risk is mitigated for three of five exposure scenarios (i.e., MOE's greater than 100):

- ◆ (#1a). Mixing/loading WSP in support of aerial application (MOE=170),
- ◆ (#2c). Mixing/loading liquid formulation in support of airblast sprayer application (MOE=290);
- ◆ (#8). Flagger of aerial liquid application (MOE = 110)

With engineering controls (closed cab and single layer clothing), risk is mitigated for:

- ◆ (#5). Airblast Sprayer, (MOE=153).

Risk is not mitigated (either with the use of additional PPE (MOE=33) or with engineering controls (MOE=95)) for:

- ◆ (#2a). Mixing/loading liquid formulation in support of aerial application.

The route-specific MOE's for the various exposure scenarios with minimum PPE, additional PPE, or engineering controls are presented below in **Table 13**.

**Table 13. Route-Specific MOE's
for Handler Exposures to Methidathion**

Exposure Scenario	DERMAL MOE			INHALATION MOE		
	Minimum PPE	PPE	Engineering Control	Minimum PPE	PPE	Engineering Control
Mixing/Loading WSP -Aerial (1a)	80	140	Not Required	33	170	NR
Mixing/Loading - WSP Groundboom (1b)	1800	NA	NR	710	NR	NR
Mixing/Loading - WSP Airblast Sprayer (1c)	710	1250	NR	290	1400	NR
Mixing/Loading Liquid Aerial (2a)	34	45	91	7	33	95
Mixing/Loading Liquid - Groundboom (2b)	770	NR	NR	150	NR	NR
Mixing/Loading Liquid Airblast (2c)	290	390	NR	60	290	830
Aerial Application - Fixed-Wing Aircraft (3)	No Data	No Data	150	No Data	No Data	120
Groundboom (4)	1250	NR	NR	250	NR	NR
Airblast Sprayer (5)	29	32	370	15	77	153

Exposure Scenario	DERMAL MOE			INHALATION MOE		
	Minimum PPE	PPE	Engineering Control	Minimum PPE	PPE	Engineering Control
Low Pressure Handwand Liquid (6)	65,000	NR	NR	9300	NR	NR
Backpack Sprayer Liquid (7)	2500	NR	NR	210	NR	NR
Flagging Aerial Applications (8)	70	71	3600	23	110	1100
<p>MOE = An MOE equal to greater than 100 generally does not exceed HED's level of risk concern for pesticide handlers (mixer/loader/applicator) exposure to methidathion.</p> <p>NR = Not Required</p> <p>Minimum PPE = Single Layer Clothing (SLC) with gloves PPE = Coveralls with SLC and glove for dermal (no gloves for flaggers); Coverall with SLC and a dust/mist respirator for inhalation</p> <p>Scenarios 1a, 2a, 3 and 8: (5lbs ai./acre x 350 acres = 1750 lb a.i./day) Scenarios 1b, 2b, and 4: (1 lb ai/acre x 80 acres = 80 lb a.i./day) Scenarios 1c, 2c, and 5: (5 lbs ai/acre x 40 acres = 200 lb a.i./day) Scenario 6: 0.5 lb ai/100 gal. at 10 gallons applied for low pressure handwand = 0.05 lb ai/day Scenario 7: 0.5 lb ai/100 gal. at 40 gallons applied for backpack sprayer liquid</p>						

3. Total Exposure (Dermal + Inhalation) Risk Characterization

The NOAEL for dermal exposure risk assessment is based on lack of systemic toxicity in a 21-day dermal study in rabbits. The NOAEL for inhalation exposure (oral equivalent) risk assessment is based on plasma, RBC and brain ChEI in an oral study in rats. Because the dermal and inhalation NOAELs are based on different toxicological endpoints (i.e., lack of systemic toxicity via the dermal route and ChEI via the oral route), it is inappropriate to add exposures for these pathways. Therefore, only route specific MOE's are appropriate for evaluation.

However, since ChEI is the principal toxicological endpoint of concern for OP's via the dermal and inhalation routes, analysis of the total MOE's were conducted for risk characterization purpose only. Data indicated that when dermal plus inhalation exposure were combined, two additional scenarios had total MOE's that were lower than HED's level of concern. For these exposure scenarios, while the route specific MOE's

were greater than 100, the dermal plus inhalation MOE's (i.e., total MOE's) less than 100 as shown below:

- ◆ (#1a). Mixing/loading WSP in support of aerial application:
Dermal MOE = 140; Inhalation MOE = 170; Total MOE = 77
(all with PPEs; no engineering controls feasible);
- ◆ (#3). Liquid aerial application with a fixed-wing aircraft:
Dermal MOE = 150; Inhalation MOE = 120; Total MOE = 67
(all with engineering controls)

A number of issues must be considered when interpreting the occupational handler risk estimates.

- ◆ The lack of chemical specific data resulted in the use of PHED data and the PHED values are approximately median exposures (i.e., central tendency point estimates) over the available data. That is, 50% of workers doing the same activity would be expected to have *higher* unit exposures, and 50% would be expected to have *lower* unit exposures. These values are derived from actual exposure studies where the same formulation types, equipment, and methods were employed as are used for methidathion. Typically, there is high variability among replicated exposure studies, often covering a range of orders of magnitude. HED considers unit exposures values derived from PHED to be no higher than average or central tendency values.
- ◆ Area treated per day for the various application methods and equipment are default values routinely used by HED. The number of acres that can be treated in an 8-hour day are considered typical to high-end values.
- ◆ Body weight is the standard 70 kg default value for adults, which is routinely used by HED. This is identified in the Exposure Factors Handbook as the mean body weight for both sexes of adults in all age groups combined, rounded to one significant figure.
- ◆ Although dermal exposures during application with handheld equipment such as a low pressure wand or backpack

sprayer were assessed using PHED data which are graded “low quality,” these data are the best currently available.

4. Data Gaps in Both Dermal and Inhalation Assessments:

Dermal and inhalation risk could not be assessed for three exposure scenarios because there are no appropriate chemical-specific data or PHED data sets available. Also, reliable information for area treated or amount handled is unavailable. These scenarios are:

- ◆ (#3). No minimum PPE and additional PPE data for aerial application of liquids with a fixed-wing aircraft (only engineering controls data are available)
- ◆ (#6). No engineering controls for liquid mixing/loading/application with a low pressure handwand (only minimum PPE and additional PPE data are available).
- ◆ (#7). No engineering controls for liquid mixing/loading/application with a backpack sprayer (only minimum PPE and additional PPE data are available).

D. Occupational Postapplication Exposure Data Sources and Assumptions

HED has determined that there is potential exposure to persons entering treated sites following application of methidathion-containing products. Postapplication exposure is anticipated to last for up to several months based on the type of activity which include reentry for scouting, irrigation, harvesting, cultivation (hoeing and weeding), pruning and propping, and sorting/packing produce. Representative crops (based on foliage type, potential for contact based on typical activity) and activity type were selected to calculate potential postapplication worker exposure and risks. Only dermal risk was assessed, because inhalation exposure is expected to be negligible. The scenarios likely to result in postapplication exposure are grouped according to similarity of crop (level of contact) and activity (transfer coefficient), and are as follows:

- ◆ scouting activities associated with cotton and with safflower (low to moderate contact level);
- ◆ hoeing, irrigation, and other activities associated with artichokes (low contact level); and

- ◆ harvesting and cultivating activities associated with citrus, kiwi fruit, longan, and carambola (high contact).

For short-term (up to 30 days) postapplication activities (scouting cotton, and safflower) the dermal NOAEL of 20 mg/kg/day was used. For intermediate-term postapplication activities (hoeing, harvesting, and packing) an oral NOAEL of 0.2 mg/kg/day was used. Since an oral dose was selected, a 30% dermal absorption factor was used to derive the dermal dose for these risk assessments.

Two postapplication DFR studies were conducted for cotton and citrus crops. DFR studies are that portion of pesticide residues that are available for transfer to humans.

The dermal dose (mg/kg/day) used for calculating the MOE's was calculated as follows:

$$\text{Dermal Dose (mg/kg/day)} = \frac{\text{DFR (}\mu\text{g/cm}^2\text{)} \times \text{Transfer Coefficient (cm}^2\text{/hr)} \times \text{Dermal Absorption} \times \text{Work Day (8 hr)}}{\text{Adjustment from }\mu\text{g to mg (1,000 }\mu\text{g)} \times \text{Body Weight (70 kg)}}$$

1. DFR Study on Cotton

The DFR study on cotton (MRID 446805-02) examined the dislodgeable residues of methidathion following three broadcast applications (of a possible maximum of four) of the pesticide at the maximum label rate (1 lb. ai/Acre) conducted at three sites in California, Texas and North Carolina. Pre-study samples demonstrated that rainfall probably affected the foliar residues prior to the final application in the Texas and North Carolina sites, however, no significant rainfall occurred at these sites in the month following the final (third) application. The dissipation rate was slower in North Carolina than in California or Texas. Review of the data suggests that environmental factors such as humidity affect the rate of residue dissipation.

Results indicated a rapid decline in the DFR over the 35-day monitoring period following the third application. The amount of dislodgeable methidathion at the California site was 1.62 $\mu\text{g/cm}^2$ at Day 0 after the final application and decreased to less than the detection limit (0.00963 $\mu\text{g/cm}^2$) on Day 21 after the last treatment. At the Texas site the residue level was 2.86 $\mu\text{g/cm}^2$ on Day 0 after the final treatment and decreased to less than the detection limit (0.00963 $\mu\text{g/cm}^2$) 28 days after treatment. The residue level for the North Carolina site was 2.03 $\mu\text{g/cm}^2$ on Day 0 after the final application and decreased to 0.0287 $\mu\text{g/cm}^2$ on

Day 35 after the treatment. HED used each individual reported value in its analysis of the data.

As the DFR values were found to be lognormally distributed, the half-lives were recalculated by linear regression which resulted in half lives of 3.8, 3.7 and 5.3 days for the California, Texas and North Carolina sites, respectively. The average half-life was 4.3 days. HED concludes from the results of this study that methidathion residues on cotton crops dissipate at different rates in different climates resulting in higher or lower MOE's and variable REI's depending on rainfall, humidity, etc. Therefore, the REIs should reflect these differences in environmental conditions.

Examination of the National Agricultural Statistical Survey (NASS) Agricultural Usage Summary indicates that it is unlikely any single scout will be exposed on seven consecutive days to cotton acreage which has been treated with methidathion. Consequently, only a short-term exposure risk assessment for scouting activities for cotton was conducted. The results of the cotton DFR studies and the REIs are presented by state in **Tables 14 and 15**.

2. DFR Study on Citrus

The DFR study conducted on citrus crops for methidathion was designed to examine the amount of residues that could be dislodged from citrus foliage following two broadcast applications at the maximum label rate (5 lb. ai/acre) of methidathion, using the 25% wettable powder (WP) (MRID 446805-01). Results for the study, which was conducted at two sites in California and one in Florida, indicate a rapid decline in the DFR over the 35-day monitoring period following the second application. The reported half lives were calculated to be 2.9, 2.0, and 0.8 days for the California 1, California 2, and Florida sites respectively. The amount of dislodgeable methidathion at the California 1 site ranged from 2.55 $\mu\text{g}/\text{cm}^2$ after the final application to 0.0146 $\mu\text{g}/\text{cm}^2$ at 35 days after treatment. Residues at the California 2 site ranged from 2.24 $\mu\text{g}/\text{cm}^2$ after the final application to 0.0266 $\mu\text{g}/\text{cm}^2$ at 35 days after treatment. At the Florida site, the residue ranged from a high of 2.28 $\mu\text{g}/\text{cm}^2$ after the final treatment to a low of non-detect (detection limit of 0.00963 $\mu\text{g}/\text{cm}^2$) at 14 days after treatment. Because heavy rainfall at the Florida site after the second application may have resulted in the residue half-life of less than one day, HED used only the California data for the risk assessment.

**Table 14. Exposure Assessment for Scout Reentry
Activity For Cotton In *NORTH CAROLINA***

Days After Treatment (DAT)	Mean DFR ^a (µg/cm ²)	Predicted DFR (µg/cm ²) ^b	Scout (Early Season) Tc = 1,000 ^c		Scout (Late Season) Tc = 4000 ^c	
			Dermal Dose ^d	MOE ^e	Dermal Dose ^d	MOE ^e
0	2.03	2.20	0.25	80	1.00	20
1	1.09	1.61	0.18	110	0.74	27
2	1.75	1.20	0.14	140	0.55	36
3	0.96	0.88	0.10	200	0.40	50
4	--	0.65	0.07	290	0.30	67
5	--	0.48	0.05	400	0.22	91
6	--	0.35	0.04	500	0.16	130
7	0.16	0.26	0.03	670	0.12	170
8	--	0.20	0.02	1,000	0.09	220
9	--	0.14	0.01	2,000	0.06	330
10	0.03	0.10	0.01	2,000	0.04	500
11	--	0.07	0.009	2,200	0.03	670
12	--	0.05	0.006	3,300	0.025	800
13	--	0.04	0.004	5,000	0.019	1100
14	0.04	0.03	0.003	6,700	0.014	1400

^aMean DFR from a chemical specific study on cotton in North Carolina (MRID 446805-02).

^bPredicted DFR values from linear regression line based on log-transferred values.

^cTransfer coefficients (Tc) estimated by the Health Effects Division (HED).

^dDermal Dose (mg/kg/day)= [(Predicted DFR µg/cm² x Transfer Coefficient (cm²/hr)) /1,000 µg/mg] x 8 hrs/day /70 kg body weight

^eMOE = NOAEL /Dermal Dose. [Dermal NOAEL = 20 mg/kg/day]. Exposure potential for this activity is less than seven days, therefor, the short-term dermal NOAEL was used. An MOE of ≥100 is required.

Table 15. Exposure Assessment for Scout Reentry Activity For Cotton In TEXAS

Days After Treatment (DAT)	Mean DFR ^a (µg/cm ²)	Predicted DFR (µg/cm ²) ^b	Scout (Early Season) Tc = 1,000 ^c		Scout (Late Season) Tc = 4,000 ^c	
			Dermal Dose ^d	MOE ^e	Dermal Dose ^d	MOE ^e
0	2.86	2.12	0.24	83	0.97	21
1	1.92	1.66	0.19	100	0.76	26
2	1.1	1.30	0.15	130	0.59	34
3	0.66	1.01	0.12	170	0.46	43
4	--	0.79	0.090	220	0.36	56
5	--	0.62	0.070	290	0.28	71
6	--	0.48	0.055	360	0.22	91
7	0.21	0.38	0.043	470	0.17	120
8	--	0.29	0.033	610	0.13	150
9	--	0.23	0.026	770	0.10	200
10	0.09	0.18	0.020	1,000	0.082	240
11	--	0.14	0.016	1,300	0.064	310
12	--	0.11	0.012	1,700	0.050	400
13	--	0.08	0.009	2,200	0.036	560
14	0.05	0.07	0.007	2,900	0.032	630

^aMean DFR from a chemical specific study on cotton in North Carolina (MRID 446805-02).
^bPredicted DFR values from linear regression line based on log-transferred values.
^cTransfer coefficients (Tc) estimated by the Health Effects Division (HED).
^dDermal Dose (mg/kg/day) = [(Predicted DFR µg/cm² x Transfer Coefficient (cm²/hr)) / 1,000 µg/mg] x 8 hrs/day / 70 kg body weight
^eMOE = NOAEL /Dermal Dose. [Dermal NOAEL = 20 mg/kg/day]. Exposure potential for this activity is less than seven days, therefore, the dermal NOAEL was used. An MOE of ≥100 is required.

HED determined that the DFR data from the study conducted in California was lognormally distributed and analysis by linear regression showed that the data were similar enough to combine the data from the two California sites , ($r^2 = 0.92$). HED believes the California data estimates to be at least as protective of the worker as the Florida data, due to the more rapid decline in DFR in Florida due to rainfall. The combined data was analyzed by linear regression and the resulting DFR's are presented in **Table 16**. Note that these data have been adjusted to reflect a typical application rate (2.8 lb ai/acre) based on BEAD data.

Table 16. Predicted DFR, Doses, and MOE's For CITRUS^a

Days After Treatment (DAT)	Incremental Predicted DFR ($\mu\text{g}/\text{cm}^2$) ^c	Risk Estimate	
		Dermal Dose ^d	MOE ^e
0	1.14	0.391	<1
1	0.92	0.315	<1
2	0.73	0.250	<1
3	0.59	0.202	<1
4	0.48	0.164	1.3
5	0.38	0.130	1..5
6	0.30	0.103	1.9
7	0.24	0.082	2.4
8	0.19	0.065	3.1
9	0.16	0.055	3.6
10	0.13	0.045	4.4
11	0.10	0.034	5.9
12	0.082	0.027	7.4
13	0.066	0.023	8.7
14 ^b	0.053	0.018	11.1
15	0.043	0.014	14.3
16	0.034	0.012	16.6
17	0.027	0.0092	21.7
18	0.022	0.0075	26.7

Days After Treatment (DAT)	Incremental Predicted DFR ($\mu\text{g}/\text{cm}^2$) ^c	Risk Estimate	
		Dermal Dose ^d	MOE ^e
19	0.018	0.0062	32.2
20	0.014	0.0048	41.6
21	0.011	0.0038	52.6
22	0.0091	0.0031	64.5
23	0.0073	0.0025	80.0
24	0.0058	0.0019	105
25	0.0047	0.0016	125

^aBased on a chemical specific study (MRID 44680501)

^bRecommended pre-harvest interval for citrus crops as stated on product label, EPA Reg. No. 100-754.

^cPredicted DFR values from linear regression line based on log-transferred values. Study data normalized from 5.0 lb ai/A to 2.8 lb ai/A application rate.

^dDermal Dose (mg/kg/day) = [(Predicted DFR $\mu\text{g}/\text{cm}^2$ x Transfer Coefficient (cm^2/hr)) / 1,000 $\mu\text{g}/\text{mg}$] x 30% dermal absorption factor x 8 hrs/day / 70 kg body weight, where Tc=10,000 cm^2/hr

^eMOE = Oral NOAEL (0.2 mg/kg/day) / Dermal Dose (mg/kg/day); MOE of ≥ 100 is required.

^fPredicted DFR = $\frac{1}{2}$ LOQ

3. Surrogate DFR Data for Other Crops

It is HED's general policy to estimate REIs for crops for which no chemical-specific data are available by assuming that the initial DFR is 20% of the applied amount, and that the dissipation rate is 10% per day. Standard residue transfer values (transfer coefficient, Tc) that are unique for various tasks and activities associated with general crop groups are also utilized for postapplication risk assessment. However, in the case of methidathion, REIs for crops that could not be represented by the categories for which data are available (cotton and citrus), were estimated using a surrogate, range-finding analysis based on existing DFR data. Surrogate DFR data were used for artichoke hoeing and irrigating, safflower scouting, and for kiwi fruit, longan, and carambola.

No chemical-specific data are available for foliar residues on safflower or artichokes. HED used the dissipation rates from the DFR studies on cotton and citrus. As methidathion is applied to these other crops primarily in California, DFR study data for methidathion for that state were used. Based on these combined data ($r^2 = 0.66$), a half-life of 3.4 days was calculated which equals a dissipation rate of 18%. As the crop application rate (1 lb artichokes; 0.5 lb safflower; 5 lb citrus; 1 lb cotton) and method were different, HED's default of 20% for initial DFR was used. The surrogate DFR data and MOE's for these crops are presented in **Table 17**.

Longan, kiwi, carambola are only registered to SLN (or 24(c)) labels and represent relatively small uses of methidathion according to the BEAD Quantitative Use Analysis (QUA) report. The QUA report dated October 27, 1999 shows that of these crops, only kiwi fruit exceeds the minimum 500 quantifiable acres, with 1,000 of 7,000 treated. Based on the known agricultural practices for trees and kiwi fruit, a DFR transfer coefficient of 10,000 cm²/hr may be used to determine postapplication exposure. As there are no studies available measuring DFR's for methidathion on these crops, but these crops are grown in California, HED used default residues and the dissipation rates (18%, which was determined by combining the California citrus and cotton studies) for the assessment; it is represented in **Table 18**.

**Table 17. Predicted DFR, Doses and MOE's
For Artichoke Hoeing, Irrigating and Safflower Scouting**

Days After Treatment (DAT)	Incremental Predicted DFR ($\mu\text{g}/\text{cm}^2$) ^a	Risk Estimates			
		Dermal Dose ^b	MOE ^c	Dermal Dose ^d	MOE ^e
		Safflower Scouting/Irrigating (Exposure less than 30 Days)		Artichoke Cultivating/Harvesting (Exposure greater than 30 Days)	
0	2.26	0.26	76.9	0.039	5
1	1.85	0.21	95.2	0.033	6
2	1.52	0.17	115	0.027	7
3	1.25	0.14	140	0.021	10
4	1.02	0.12	170	0.018	11
5	0.84	0.10	200	0.015	13
6	0.69	0.078	250	0.012	17
7	0.56	0.064	310	0.010	20
8	0.46	0.052	380	0.0078	26
9	0.38	0.043	460	0.0065	31
10	0.31	0.035	570	0.0053	38
11	0.25	0.029	700	0.0043	47
12	0.21	0.024	830	0.0036	56
13	0.17	0.019	1050	0.0029	69
14	0.14	0.016	1250	0.0024	83
15	0.12	0.014	1429	0.0020	100
19	0.052	0.0059	3400	0.00086	232

^aDAT zero (0), 2.26 mg/cm² = 20% Residual and 18% dissipation rate at application rate of 1 lb ai/acre. The average 18% /day dissipation rate is derived by combining the results of the cotton/citrus California DFR studies.

^bDermal Dose (mg/kg/day) = [(Predicted DFR $\mu\text{g}/\text{cm}^2$ x Transfer Coefficient (cm²/hr)) / 1,000 $\mu\text{g}/\text{mg}$] x 8 hrs/day / 70 kg body weight, where **Tc=1,000 cm²/hr** (dermal absorption factor not required).

^cMOE = **Dermal NOAEL (20 mg/kg/day)** / Dermal Dose (mg/kg/day); MOE of ≥ 100 is required.

^dDermal Dose (mg/kg/day) = [(Predicted DFR $\mu\text{g}/\text{cm}^2$ x Transfer Coefficient (cm²/hr)) / 1,000 $\mu\text{g}/\text{mg}$] x 30% dermal absorption factor x 8 hrs/day / 70 kg body weight, where **Tc=500 cm²/hr**

^eMOE = **Oral NOAEL (0.2 mg/kg/day)** / Dermal Dose (mg/kg/day); MOE of ≥ 100 is required.

**Table 18. Surrogate DFR, Doses and MOE's
For Kiwi Fruit, Longan, and Carambola**

Days After Treatment (DAT)	Incremental Surrogate DFR ($\mu\text{g}/\text{cm}^2$) ^a	Short-Term Exposure		Intermediate-Term Exposure	
		Dermal Dose ^b	MOE ^c	Dermal Dose ^d	MOE ^e
0	4.52	5.17	3.9	1.55	<1
1	2.71	4.24	4.7	1.27	<1
2	3.04	3.47	5.8	1.04	<1
3	2.49	2.85	7.0	0.86	<1
4	2.04	2.33	8.6	0.69	<1
5	1.68	1.91	10	0.57	<1
6	1.37	1.57	13	0.47	<1
7	1.13	1.29	16	0.39	<1
8	0.92	1.05	19	0.32	<1
9	0.76	0.86	23	0.26	<1
10	0.62	0.71	28	0.21	<1
11	0.51	0.58	34	0.17	1.2
12	0.42	0.48	42	0.14	1.4
13	0.34	0.39	51	0.12	1.7
14	0.28	0.32	63	0.096	2.1
15	0.23	0.26	77	0.078	2.6
16	0.19	0.21	95	0.063	3.2
17	0.15	0.17	111	0.051	3.9
18	0.13	0.14	142	0.042	4.8
19	0.10	0.11	181	0.033	6.1
20	0.09	0.10	200	0.030	6.7
21	0.07	0.080	250	0.024	8.3
22	0.06	0.068	294	0.020	10
23	0.05	0.057	350	0.017	12
24	0.04	0.046	435	0.014	14
25	0.03	0.034	588	0.009	20
26	0.03	0.029	689	0.008	25
27	0.02	0.024	833	0.0072	28
28	0.02	0.019	1,052	0.0057	35
29	0.01	0.016	1,250	0.0048	42
30	0.01	0.013	1,538	0.0039	51
31	0.01	0.010	2,000	0.0030	67
32	0.01	0.0090	2,222	0.0027	74
33	0.01	0.0074	2,702	0.0022	91
34	0.01	0.0060	3,333	0.0018	111
35	0.00				

^aDefault DFR @ 2 lbs.a.i./acre with 20% residual and 18% Dissipation/Day

^bDermal Dose (mg/kg/day)= [(Predicted DFR $\mu\text{g}/\text{cm}^2$ x Transfer Coefficient (cm^2/hr))/1,000 $\mu\text{g}/\text{mg}$] x 8 hrs/day /70 kg body weight, where Tc=10,000 cm^2/hr .

^cMOE = Dermal NOAEL (20 mg/kg/day) /Dermal Dose (mg/kg/day); MOE of ≥ 100 is required.

^dDermal Dose (mg/kg/day)= [(Predicted DFR $\mu\text{g}/\text{cm}^2$ x Transfer Coefficient (cm^2/hr)) /1,000 $\mu\text{g}/\text{mg}$] x 30% dermal absorption factor x 8 hrs/day /70 kg body weight, where Tc=10,000 cm^2/hr

^eMOE = Oral NOAEL (0.2 mg/kg/day) /Dermal Dose (mg/kg/day); MOE of ≥ 100 is required.

Because it is difficult to predict exactly what activities (to determine the corresponding transfer coefficients) would be performed on crops other than those already categorized, a range of transfer coefficients of 1,000 cm^2/hr to 10,000 cm^2/hr was used to bracket the potential job/task activities. Methidathion is applied to safflower and artichoke crops. Because safflower is mechanically planted and harvested, and artichokes, according to acknowledged agricultural practices, are only treated during the pre-bud stage, a low dermal transfer coefficient, according to HED policy, has been assigned to these crops. Safflower scouting and early season activities for artichoke are assigned a dermal transfer coefficient of 1,000 cm^2/hr . Reentry into safflower fields is generally a concern only for scout/consultants.

Methidathion, according to registered product labeling, is applied to nut trees, pome and stone fruit trees, and olive trees while dormant or in the bud stage. Therefore, there would be no foliar residue, *per se*, when the chemical is applied prior to foliation. Based on these agricultural practices, there should be negligible postapplication chemical exposure to workers at this stage of growth, unless those workers are performing such activities as pruning, etc., which would bring them into contact with the limbs of the trees. HED does not have sufficient data to estimate exposure for pruning bare trees. However, an exposure study of citrus workers pruning trees with leaves found the foliar transfer rate to be $\sim 1400 \text{ cm}^2/\text{hr}$., therefore, pruning bare trees would result in even less exposure.

E. Occupational Postapplication Risk Characterization

Scouting activities associated with cotton are presumed to have a short-term exposure potential since it is unlikely any single scout will be exposed on seven consecutive days to cotton acreage which has been treated with methidathion. Consequently, for scouting activities associated with cotton, the MOE's for REIs were derived by comparison of dermal exposure estimates (i.e., dermal dose) against a NOAEL of 20 mg/kg/day from a dermal toxicity study in rabbits.

The MOE's for REIs for other crops/activities were considered to have the potential for a longer exposure period lasting up to several months. Consequently, MOE's for REIs for these activities were derived by a comparison of dermal dose (adjusted for 30% dermal absorption) against an oral NOAEL of 0.2 mg/kg/day.

An MOE equal to or greater than 100 does not exceed HED's level of risk concern for postapplication exposure to methidathion.

1. Cotton Scouting

HED has concluded that it is unlikely for scouts to be exposed for seven days or more to cotton acreage which has been treated with methidathion, therefore, the dermal NOAEL of 20 mg/kg/day was used to calculate the MOE's. For cotton crops, scout can enter the treated acreage one DAT for early season scouting in North Carolina (MOE = 110) and Texas (MOE=100) and for late season scouting, six days after treatment in North Carolina (MOE=130) and seven days after treatment in Texas (MOE=120). The late season scouting activity has higher exposure potential due to the presence of increased cotton foliage, therefore, requires a longer REI (i.e., six to seven days post treatment). These REIs are shown in **Tables 14 and 15**.

2. Citrus Harvesting

Citrus harvesting is anticipated to occur anytime during the year for different varieties and different growing regions, and therefore, harvesting activities can last longer than 30 days. Consequently, the NOAEL of 0.2 mg/kg/day (based on an oral study) with the 30% dermal absorption factor was used to calculate the MOE's. Risk estimates indicate that workers can enter the treated acreage 24 days post treatment (MOE=122) as shown in **Table 16**.

3. Other Crops and Activities

A surrogate assessment was conducted for crops that could not be categorized with the above (artichoke cultivating/harvesting and safflower scouting/irrigating).

For exposure from safflower scouting/irrigating activities that have an associated transfer coefficient as low as 1,000 cm²/hr, an MOE of 115 (i.e., >100) is attained by the 2nd DAT. For artichoke cultivation/harvesting and a transfer coefficient of 500 cm²/hr results in a MOE of 100 on the 15th DAT. These REIs are shown in **Table 17**.

For exposure from other crops/activities (kiwi fruit, longan, and carambola harvesting) that have an associated transfer coefficient as high as 10,000 cm²/hr, MOE's do not reach 100 until the 17st day for activities up to 30 days, and the 34th day for activities lasting longer than 30 days after the last application as shown in **Table 18**.

Table 19. Summary of the Results of Occupational Postapplication Risk Assessments

Crop	Post App. Activity	Rate (lb a.i./A)	Tc (cm ² /hr)	MOE (> 100)
<u>Short-Term Exposure Activities</u>				
Cotton (NC)	Early scouting	1	1000	DAT 1
	Late scouting	1	4000	DAT 6
Cotton (TX)	Early scouting	1	1000	DAT 1
	Late scouting	1	4000	DAT 7
Safflower	Scouting	1	1000	DAT 2
Other crops	Harvesting	2	10,000	DAT 17
<u>Intermediate-Term Exposure Activities</u>				
Citrus	Harvesting	2.8	10,000	DAT 24
Artichoke	Cultivation/Harvesting	1	500	DAT 15
Other Crops	Harvesting	2	10,000	DAT 34

A number of issues must be considered when interpreting the postapplication risk estimates. Two variables are used in the calculations for postapplication exposure DFR and the residue transfer coefficient. The relative value of each of these parameters is described below:

- ◆ Chemical-specific DFR data were used to complete this assessment for cotton and citrus. These data, used to estimate REIs, have undergone review and have been considered acceptable by the Agency. However, data were not available for all crops; therefore, extrapolation was necessary. The extrapolation process was not conservative in that average, rather than minimum or standard value initial residue levels and dissipation rates were used to estimate surrogate (predicted) DFR's.
- ◆ Transfer coefficients used to calculate postapplication risk are based on best professional judgement due to lack of data specific to each crop/activity combination. These transfer coefficients are the default transfer coefficient recommended by HED's Science Advisory Council for Exposure (Draft Policy.003, May 7, 1998).

F. Residential Exposure

At the present time, there are no registered uses of methidathion in residential setting and none of the registered occupational uses are likely to involve applications to public access areas or at residential sites. There may be potential for spray drift associated with the aerial applications or other high volume spray in densely populated agricultural areas where peripheral residential exposures and/or exposure to farm worker children could occur. An assessment of the potential exposure and risk from spray drift associated with agricultural use of methidathion has not been included in this document. The Agency is in the process of developing guidance and procedures characterizing these kind of exposures. This guidance will be included in our upcoming revised SOP's for Residential Exposure Assessment.

G. Incident Reports

The total number of poisoning cases due to methidathion exposure reported to the Poison Control Center and the California Pesticide Illness Surveillance Program is small in relation to other OP and carbamate pesticides. Methidathion was not on the list of top 20 chemicals for which the National Pesticide Telecommunications Network (NPTN) received calls from 1984 through 1991, inclusive. However, methidathion ranked third highest in number of poisoning incidents and health care referrals per 1000 applications, based on California and poison control center data.

VI. AGGREGATE RISK ASSESSMENT AND RISK CHARACTERIZATION

A. Acute Aggregate Risk

Acute aggregate risk estimates do not exceed HED's level of concern. The aggregate acute dietary risk estimates include exposure to methidathion residues in food and water. Exposure (food only) to residues of methidathion based on a refined Tier 3 probabilistic analysis, represents 64% of the acute PAD at the 99.9th percentile of exposure for the most highly exposed population subgroup (nursing infants, <1 year). Exposure for the US population represents 16% of the acute PAD. Using conservative screening-level models and limited monitoring data, the estimated maximum peak concentration of methidathion in surface water is 5.6 ppb and the EEC for groundwater is 0.4 ppb. By comparing the peak methidathion EECs of 6 ppb for surface water and maximum 5 ppb for ground water, based on monitoring data, to the acute DWLOC, the acute DWLOC did not exceed the Agency's level of concern for any subgroups. Consequently, these EECs are less than DWLOC for exposure to methidathion in drinking water as contribution to aggregate acute dietary risk. Based on the available data, HED concludes with reasonable certainty that no harm to any population will result from acute dietary exposure to methidathion.

B. Chronic Aggregate Risk

Chronic (non-cancer) aggregate risk estimates do not exceed HED's level of concern. The aggregate chronic dietary risk estimates include exposure to methidathion residues in food and water. No long-term residential exposure scenarios were identified. Exposure (food only) to methidathion based on a Tier 2 DRES analysis, represents 23% of the chronic PAD for the most highly exposed population subgroup (children one to six years of age). Exposure for the US population represents 9% of the chronic PAD. Using conservative screening-level models and limited monitoring data the maximum annual average of concentration of methidathion in surface water is 0.6 ppb and the EEC for groundwater is 0.4 ppb. Chronic concentrations of methidathion in surface water and ground water are expected to be less than 1 ppm, thus, the chronic DWLOCs also did not exceed the Agency's level of concern. These EECs are less than the DWLOC for exposure to methidathion in drinking water as contribution to aggregate chronic dietary risk. Based on the available data, HED concludes with reasonable certainty that no harm to any population will result from acute dietary exposure to methidathion.

VII. ENDOCRINE EFFECTS

The Agency is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) “may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect.” The Agency is currently working with interested stakeholders, including government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed three years from the passage of the FQPA (August 3, 1996) to implement this program. At that time the Agency may require further testing of methidathion for endocrine effects.

VIII. CUMULATIVE EXPOSURE AND RISK

It has been determined that the OP’s share a common mechanism of toxicity; the inhibition of cholinesterase activity. As required by FQPA, a cumulative assessment will need to be conducted to evaluate the risk from food, water and non-occupational exposure resulting from all uses of OPs. Currently, the Agency is developing the draft methodology needed to conduct such an assessment with guidance/advice provided by the FIFRA Science Advisory Panel (SAP). It is anticipated that this draft methodology will be available for comment and scientific review in 1999/2000. Consequently, the risks summarized in this document are only for methidathion.

IX. DATA NEEDS

Field Crop Trial data on cotton gin-byproducts (OPPTS 860.1500). The Agency currently recognizes cotton gin products (commonly called gin trash which include the plant residues from ginning cotton consisting of burrs, leaves, stems, lint, immature seeds, and sand and/or dirt) as a RAC (OPPTS 860.1500). Data depicting the magnitude of methidathion residues of concern in/on cotton gin byproducts following application(s) of a representative formulation according to the maximum registered use patterns are required. Cotton must be harvested by commercial equipment (stripper and mechanical picker) to provide an adequate representation of plant residue for the ginning process. A minimum of three field trials for each type of harvesting (stripper and mechanical picker) are required, for a total of six field trials. An appropriate tolerance for this RAC should be proposed once acceptable data have been submitted and evaluated.

No additional toxicology data are needed to satisfy standard OPPTS Series 870 Guideline requirements. Although there was a decision not to require a developmental neurotoxicity study for methidathion, the Agency on September 10, 1999, issued a Data-Call-In notice requiring a developmental neurotoxicity study for all OP's.

The need for additional data for occupational exposure will be determined when HED and the Special Review and Reregistration Division (SRRD) consider risk mitigation/regulatory options.